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     FILE 'USPATFULL' ENTERED AT 11:30:45 ON 21 MAY 2003
L1          2233 S FIBRINOGEN AND WOUND
L2            92 S L1/CLM
L3            40 S L1/AB
L4            21 S L2 AND L3
L5          1989 S FIBROBLAST AND FIBRINOGEN
L6            26 S FIBROBLAST MIGRATION AND FIBRINOGEN
L7             0 S L4 AND L6
L8          8067 S FIBRINOGEN
L9           116 S PREPAR? (2S) L8 (3S) GLYCIN?
L10          115 S PREPAR? (1S) L8 (1S) GLYCIN?
L11            0 S PREPAR? (1S) L8 (1S) GLYCIN?  (1S) PLAMA
L12           69 S PREPAR? (1S) L8 (1S) GLYCIN?  (1S) PLASMA
L13           43 S L12 (1S) PRECIPITAT?

=> s l13 and l1
L14           28 L13 AND L1

=> s fibrinogen (1s) wound
L15          623 FIBRINOGEN (1S) WOUND

=> s l15 and l13
L16           25 L15 AND L13

=> d 1-25

L16  ANSWER 1 OF 25  USPATFULL
AN      2003:133474  USPATFULL
TI      Storage-stable human fibrinogen solutions
IN      Woolverton, Christopher J., Kent, OH, UNITED STATES
PI      US 2003091559      A1   20030515
AI      US 2002-267104     A1   20021003 (10)
PRAI    US 2001-326962P         20011003 (60)
DT      Utility
FS      APPLICATION
LN.CNT 942
INCL    INCLM: 424/094.640
NCL     NCLM:  424/094.640
IC      [7]
        ICM: A61K038-48

L16  ANSWER 2 OF 25  USPATFULL
AN      2003:133473  USPATFULL
TI      Storage-stable fibrinogen solutions
IN      Woolverton, Christopher J., Kent, OH, UNITED STATES
PI      US 2003091558      A1   20030515
AI      US 2002-263987     A1   20021003 (10)
PRAI    US 2001-326963P         20011003 (60)
DT      Utility
FS      APPLICATION
LN.CNT 1021
INCL    INCLM: 424/094.640
NCL     NCLM:  424/094.640
IC      [7]
        ICM: A61K038-48

L16  ANSWER 3 OF 25  USPATFULL
AN      2003:112540  USPATFULL
TI      Method for producing a preparation based on fibrinogen and fibronectin
        as well as protein compositions obtainable according to this method
IN      Seelich, Thomas, Vienna, AUSTRIA
        Broermann, Ralf, Vienne, AUSTRIA
PI      US 2003077270      A1   20030424
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2/9/99

AI US 2002-300388 A1 20021119 (10)
RLI Continuation of Ser. No. US 2000-502029, filed on 10 Feb 2000, PENDING
PRAI AT 1999-206 19990212
DT Utility
FS APPLICATION
LN.CNT 977
INCL INCLM: 424/094.630
NCL NCLM: 424/094.630
IC [7]
ICM: A61K038-48
CAS INDEXING IS AVAILABLE FOR THIS PATENT.

L16 ANSWER 4 OF 25 USPATFULL
AN 2002:343578 USPATFULL
TI Hemostatic polymer useful for rapid blood coagulation and hemostasis
IN Cochrum, Kent C., Davis, CA, UNITED STATES
Gunther, Robert A., Davis, CA, UNITED STATES
Jemtrud, Susan A., San Francisco, CA, UNITED STATES
Beninsig, Franklin M., Sacramento, CA, UNITED STATES
PI US 2002197302 A1 20021226
AI US 2002-153336 A1 20020522 (10)
RLI Continuation-in-part of Ser. No. US 1999-290846, filed on 13 Apr 1999, ABANDONED Division of Ser. No. US 1999-438072, filed on 10 Nov 1999, PENDING
PRAI US 1998-108185P 19981112 (60)
DT Utility
FS APPLICATION
LN.CNT 2273
INCL INCLM: 424/445.000
NCL NCLM: 424/445.000
IC [7]
ICM: A61L015-00
CAS INDEXING IS AVAILABLE FOR THIS PATENT.

L16 ANSWER 5 OF 25 USPATFULL
AN 2002:307599 USPATFULL
TI METHOD FOR PRODUCING FIBRONECTIN AND FIBINOGEN COMPOSITION USING A POLYALKYLENE GLYCOL AND GLYCINE OR B-ALANINE
IN Seelich, Thomas, Vienna, AUSTRIA
Broermann, Ralf, Vienna, AUSTRIA
PI US 2002172718 A1 20021121
AI US 2000-502029 A1 20000210 (9)
DT Utility
FS APPLICATION
LN.CNT 976
INCL INCLM: 424/520.000
INCLS: 424/094.640
NCL NCLM: 424/520.000
NCLS: 424/094.640
IC [7]
ICM: A61K035-12

L16 ANSWER 6 OF 25 USPATFULL
AN 2002:213423 USPATFULL
TI Medicament for topical application
IN Eibl, Johann, Wien, AUSTRIA
PI US 2002114796 A1 20020822
AI US 2001-998575 A1 20011116 (9)
RLI Continuation of Ser. No. WO 2000-AT141, filed on 19 May 2000, UNKNOWN
PRAI AT 1999-89599 19990519
DT Utility
FS APPLICATION
LN.CNT 1547
INCL INCLM: 424/094.100

INCLS: 424/094.640; 424/094.500
NCL NCLM: 424/094.100
NCLS: 424/094.640; 424/094.500
IC [7]
ICM: A61K038-48
ICS: A61K038-53
CAS INDEXING IS AVAILABLE FOR THIS PATENT.

L16 ANSWER 7 OF 25 USPATFULL
AN 2002:32204 USPATFULL
TI Purification of fibrinogen from fluids by precipitation and hydrophoic chromatography
IN McCreath, Graham, Edinburgh, UNITED KINGDOM
Michael, Udell N., Edinburgh, UNITED KINGDOM
PI US 2002019025 A1 20020214
AI US 2001-814371 A1 20010322 (9)
RLI Continuation of Ser. No. WO 1999-GB3193, filed on 24 Sep 1999, UNKNOWN
PRAI GB 1998-20847 19980924
GB 1998-20848 19980924
GB 1998-20845 19980924
US 1998-103319P 19981007 (60)
US 1998-103321P 19981007 (60)
DT Utility
FS APPLICATION
LN.CNT 1322
INCL INCLM: 435/068.100
INCLS: 800/007.000; 530/350.000
NCL NCLM: 435/068.100
NCLS: 800/007.000; 530/350.000
IC [7]
ICM: C12P021-06
ICS: C12N009-64; C07K017-00; C12P021-00; C07K001-00
CAS INDEXING IS AVAILABLE FOR THIS PATENT.

L16 ANSWER 8 OF 25 USPATFULL
AN 2001:112501 USPATFULL
TI Fibrin sealant compositions and methods for utilizing same
IN Edwardson, Peter A. D., Chester, United Kingdom
Fairbrother, John E., Clwyd, United Kingdom
Gardner, Ronald S., Clwyd, United Kingdom
Hollingsbee, Derek A., South Wirral, United Kingdom
Cederholm-Williams, Stewart A., Oxford, United Kingdom
PA Bristol-Myers Squibb Company, New York, NY, United States (U.S. corporation)
PI US 6262236 B1 20010717
AI US 2000-514169 20000228 (9)
RLI Continuation of Ser. No. US 1997-997265, filed on 23 Dec 1997, now patented, Pat. No. US 6048966 Continuation of Ser. No. US 1993-138674, filed on 18 Oct 1993, now patented, Pat. No. US 5750657 Continuation-in-part of Ser. No. US 1992-958212, filed on 8 Oct 1992, now abandoned
DT Utility
FS GRANTED
LN.CNT 1429
INCL INCLM: 530/382.000
INCLS: 530/381.000; 424/530.000; 435/212.000; 435/214.000; 435/217.000
NCL NCLM: 530/382.000
NCLS: 424/530.000; 435/212.000; 435/214.000; 435/217.000; 530/381.000
IC [7]
ICM: A61K035-14
ICS: A61K038-00; C07K001-00; C07K014-00; C07K016-00
EXF 530/381; 530/382; 530/383; 530/384; 435/212; 435/214; 435/217; 435/529; 424/530; 514/8; 514/12; 514/21
CAS INDEXING IS AVAILABLE FOR THIS PATENT.

L16 ANSWER 9 OF 25 USPATFULL
AN 2000:77025 USPATFULL
TI Method of making a composition comprising a fibrin monomer
IN Edwardson, Peter A. D., Chester, United Kingdom
Fairbrother, John E., Clwyd, United Kingdom
Gardner, Ronald S., Clwyd, United Kingdom
Hollingsbee, Derek A., South Wirral, United Kingdom
Cederholm-Williams, Stewart A., Oxford, United Kingdom
PA Bristol-Myers Squibb Company, Skillman, NJ, United States (U.S. corporation)
PI US 6077507 20000620
AI US 1997-832320 19970326 (8)
RLI Division of Ser. No. US 1995-450829, filed on 25 May 1995, now patented, Pat. No. US 5770194 which is a division of Ser. No. US 1993-138674, filed on 18 Oct 1993, now patented, Pat. No. US 5750657 which is a continuation-in-part of Ser. No. US 1992-958212, filed on 8 Oct 1992, now abandoned
DT Utility
FS Granted
LN.CNT 1586
INCL INCLM: 424/094.640
INCLS: 424/529.000; 424/530.000; 514/002.000; 514/021.000; 435/214.000; 530/382.000
NCL NCLM: 424/094.640
NCLS: 424/529.000; 424/530.000; 435/214.000; 514/002.000; 514/021.000; 530/382.000
IC [7]
ICM: A61K038-48
EXF 530/382; 424/94.64; 424/529; 424/530; 514/2; 514/21; 435/214
CAS INDEXING IS AVAILABLE FOR THIS PATENT.

L16 ANSWER 10 OF 25 USPATFULL
AN 2000:44205 USPATFULL
TI Fibrin sealant compositions and methods for utilizing same
IN Edwardson, Peter A. D., Chester, United Kingdom
Fairbrother, John E., Clwyd, United Kingdom
Gardner, Ronald S., Clwyd, United Kingdom
Hollingsbee, Derek A., South Wirral, United Kingdom
Cederholm-Williams, Stewart A., Oxford, United Kingdom
PA Bristol-Myers Squibb Company, Skillman, NJ, United States (U.S. corporation)
PI US 6048966 20000411
AI US 1997-997265 19971223 (8)
RLI Continuation of Ser. No. US 1993-138674, filed on 18 Oct 1993, now patented, Pat. No. US 5750657 which is a continuation-in-part of Ser. No. US 1992-958212, filed on 8 Oct 1992, now abandoned
DT Utility
FS Granted
LN.CNT 1422
INCL INCLM: 530/382.000
INCLS: 530/381.000; 424/094.640; 424/529.000; 424/530.000; 435/212.000; 435/214.000; 435/217.000; 514/008.000; 514/012.000; 514/021.000
NCL NCLM: 530/382.000
NCLS: 424/094.640; 424/529.000; 424/530.000; 435/212.000; 435/214.000; 435/217.000; 530/381.000
IC [7]
ICM: A61K035-14
EXF 530/380; 530/381; 530/382; 424/94.64; 424/529; 424/530; 435/212; 435/214; 435/217; 514/12; 514/8; 514/21
CAS INDEXING IS AVAILABLE FOR THIS PATENT.

L16 ANSWER 11 OF 25 USPATFULL
AN 1999:121322 USPATFULL

TI Fibrin sealant compositions and methods for utilizing same
IN Edwardson, Peter A. D., Chester, United Kingdom
Fairbrother, John E., Clwyd, United Kingdom
Gardner, Ronald S., Clwyd, United Kingdom
Hollingsbee, Derek A., South Wirral, United Kingdom
Cederholm-Williams, Stewart A., Oxford, United Kingdom
PA Bristol-Myers Squibb Company, Skillman, NJ, United States (U.S. corporation)
PI US 5962420 19991005
AI US 1998-59068 19980413 (9)
RLI Division of Ser. No. US 1993-138674, filed on 18 Oct 1993, now patented, Pat. No. US 5750657 which is a continuation-in-part of Ser. No. US 1992-958212, filed on 8 Oct 1992, now abandoned
DT Utility
FS Granted
LN.CNT 1470
INCL INCLM: 514/021.000
INCLS: 514/012.000; 424/529.000; 424/530.000; 530/380.000; 530/381.000; 530/382.000
NCL NCLM: 514/021.000
NCLS: 424/529.000; 424/530.000; 514/012.000; 530/380.000; 530/381.000; 530/382.000
IC [6]
ICM: A61K038-36
EXF 514/12; 514/21; 424/530; 424/529; 530/380; 530/381; 530/382
CAS INDEXING IS AVAILABLE FOR THIS PATENT.

L16 ANSWER 12 OF 25 USPATFULL
AN 1999:121307 USPATFULL
TI Storage-stable fibrinogen preparations
IN Seelich, Thomas, Vienna, Austria
PA Immuno Aktiengesellschaft, Vienna, Austria (non-U.S. corporation)
PI US 5962405 19991005
AI US 1997-838975 19970423 (8)
PRAI DE 1996-19617369 19960430
DT Utility
FS Granted
LN.CNT 722
INCL INCLM: 514/002.000
INCLS: 530/382.000; 530/383.000; 424/101.000
NCL NCLM: 514/002.000
NCLS: 530/382.000; 530/383.000
IC [6]
ICM: A61K038-00
ICS: C07K005-00; C07K007-00
EXF 530/382-383; 514/2; 424/101
CAS INDEXING IS AVAILABLE FOR THIS PATENT.

L16 ANSWER 13 OF 25 USPATFULL
AN 1999:120930 USPATFULL
TI Solid compositions of fibrin monomer
IN Edwardson, Peter A. D., Chester, United Kingdom
Fairbrother, John E., Clwyd, United Kingdom
Gardner, Ronald S., Clwyd, United Kingdom
Hollingsbee, Derek A., South Wirral, United Kingdom
Cederholm-Williams, Stewart A., Oxford, United Kingdom
PA Bristol-Myers Squibb Company, Skillman, NJ, United States (U.S. corporation)
PI US 5962026 19991005
AI US 1995-456127 19950531 (8)
RLI Division of Ser. No. US 1993-138674, filed on 18 Oct 1993, now patented, Pat. No. US 5750657 which is a continuation-in-part of Ser. No. US 1992-958212, filed on 8 Oct 1992, now abandoned
DT Utility

FS Granted
LN.CNT 1561
INCL INCLM: 424/529.000
INCLS: 424/530.000; 514/002.000; 514/021.000; 530/382.000
NCL NCLM: 424/529.000
NCLS: 424/530.000; 514/002.000; 514/021.000; 530/382.000
IC [6]
ICM: A61K035-14
EXF 530/382; 514/2; 514/21; 424/529; 424/530

L16 ANSWER 14 OF 25 USPATFULL
AN 1998:108262 USPATFULL
TI Fibrin sealant compositions and methods for utilizing same
IN Edwardson, Peter A. D., Chester, United Kingdom
Fairbrother, John E., Clwyd, United Kingdom
Gardner, Ronald S., Clwyd, United Kingdom
Hollingsbee, Derek A., South Wirral, United Kingdom
Cederholm-Williams, Stewart A., Oxford, United Kingdom
PA Bristol-Myers Squibb Company, Skillman, NJ, United States (U.S. corporation)
PI US 5804428 19980908
AI US 1998-52340 19980331
RLI Division of Ser. No. US 1993-138674, filed on 18 Oct 1993, now patented, Pat. No. US 5750657 which is a continuation-in-part of Ser. No. US 1992-958212, filed on 8 Oct 1992, now abandoned
DT Utility
FS Granted
LN.CNT 1545
INCL INCLM: 435/212.000
INCLS: 435/214.000; 435/217.000; 514/002.000; 514/006.000; 514/012.000; 514/021.000; 530/381.000; 530/382.000; 530/383.000; 530/384.000; 424/094.640; 424/529.000; 424/530.000
NCL NCLM: 435/212.000
NCLS: 424/094.640; 424/529.000; 424/530.000; 435/214.000; 435/217.000; 514/002.000; 514/006.000; 514/012.000; 514/021.000; 530/381.000; 530/382.000; 530/383.000; 530/384.000
IC [6]
ICM: C12N009-48
EXF 435/214; 435/212; 435/217; 514/2; 514/6; 514/12; 514/21; 530/382; 530/381; 530/383; 530/384; 424/94.64; 424/529; 424/530
CAS INDEXING IS AVAILABLE FOR THIS PATENT.

L16 ANSWER 15 OF 25 USPATFULL
AN 1998:75564 USPATFULL
TI Fibrin sealant compositions and methods for utilizing same
IN Edwardson, Peter A. D., Chester, United Kingdom
Fairbrother, John E., Clwyd, United Kingdom
Gardner, Ronald S., Clwyd, United Kingdom
Hollingsbee, Derek A., South Wirral, United Kingdom
Cederholm-Williams, Stewart A., Oxford, United Kingdom
PA Bristol-Myers Squibb Company, Skillman, NJ, United States (U.S. corporation)
PI US 5773418 19980630
AI US 1997-975095 19971120 (8)
RLI Continuation of Ser. No. US 1993-138674, filed on 18 Oct 1993 which is a continuation-in-part of Ser. No. US 1992-958212, filed on 8 Oct 1992, now abandoned
DT Utility
FS Granted
LN.CNT 1578
INCL INCLM: 514/021.000
INCLS: 514/012.000; 424/094.640; 424/529.000; 530/382.000
NCL NCLM: 514/021.000
NCLS: 424/094.640; 424/529.000; 514/012.000; 530/382.000

IC [6]
ICM: A61K035-14
ICS: A61K038-36
EXF 514/21; 514/12; 424/529; 424/94.64; 530/382
CAS INDEXING IS AVAILABLE FOR THIS PATENT.

L16 ANSWER 16 OF 25 USPATFULL
AN 1998:72238 USPATFULL
TI Fibrin sealant compositions and methods for utilizing same
IN Edwardson, Peter A. D., Chester, United Kingdom
Fairbrother, John E., Clwyd, United Kingdom
Gardner, Ronald S., Clwyd, United Kingdom
Hollingsbee, Derek A., South Wirral, United Kingdom
Cederholm-Williams, Stewart A., Oxford, United Kingdom
PA Bristol-Myers Squibb Company, Skillman, NJ, United States (U.S. corporation)
PI US 5770194 19980623
AI US 1995-450829 19950525 (8)
RLI Division of Ser. No. US 1993-138674, filed on 18 Oct 1993 which is a continuation-in-part of Ser. No. US 1992-958212, filed on 8 Oct 1992, now abandoned
DT Utility
FS Granted
LN.CNT 1547
INCL INCLM: 424/094.640
INCLS: 424/529.000; 424/530.000; 530/382.000; 514/002.000; 514/021.000
NCL NCLM: 424/094.640
NCLS: 424/529.000; 424/530.000; 514/002.000; 514/021.000; 530/382.000
IC [6]
ICM: A61K038-48
EXF 424/529; 424/530; 424/94.64; 530/383; 514/2; 514/21
CAS INDEXING IS AVAILABLE FOR THIS PATENT.

L16 ANSWER 17 OF 25 USPATFULL
AN 1998:65194 USPATFULL
TI Nondynamic fibrin monomer on bandages, sutures, prostheses and dressings
IN Edwardson, Peter A. D., Chester, United Kingdom
Fairbrother, John E., Clwyd, United Kingdom
Gardner, Ronald S., Shotton, United Kingdom
Hollingsbee, Derek A., South Wirral, United Kingdom
Cederholm-Williams, Stewart A., Oxford, United Kingdom
PA Bristol-Myers Squibb Company, Skillman, NJ, United States (U.S. corporation)
PI US 5763411 19980609
AI US 1995-489521 19950602 (8)
RLI Division of Ser. No. US 1993-138674, filed on 18 Oct 1993 which is a continuation-in-part of Ser. No. US 1992-958212, filed on 8 Oct 1992, now abandoned
DT Utility
FS Granted
LN.CNT 1567
INCL INCLM: 514/021.000
INCLS: 514/012.000; 530/382.000; 424/529.000; 424/530.000; 424/443.000; 424/445.000; 424/447.000; 602/041.000; 602/042.000; 602/043.000; 602/048.000; 623/066.000
NCL NCLM: 514/021.000
NCLS: 424/443.000; 424/445.000; 424/447.000; 424/529.000; 424/530.000; 514/012.000; 530/382.000; 602/041.000; 602/042.000; 602/043.000; 602/048.000
IC [6]
ICM: A61K038-36
EXF 530/382; 514/2; 514/21; 514/12; 424/529; 424/530; 424/443; 424/445; 424/447; 602/41; 602/42; 602/43; 602/48; 602/1; 623/66
CAS INDEXING IS AVAILABLE FOR THIS PATENT.

L16 ANSWER 18 OF 25 USPATFULL
AN 1998:65193 USPATFULL
TI Kit for preparing a fibrin sealant
IN Edwardson, Peter A. D., Chester, United Kingdom
Fairbrother, John E., Clwyd, United Kingdom
Gardner, Ronald S., Clwyd, United Kingdom
Hollingsbee, Derek A., South Wirral, United Kingdom
Cederholm-Williams, Stewart A., Oxford, United Kingdom
PA Bristol-Myers Squibb Company, Skillman, NJ, United States (U.S. corporation)
PI US 5763410 19980609
AI US 1995-460738 19950602 (8)
RLI Division of Ser. No. US 1993-138674, filed on 18 Oct 1993 which is a continuation-in-part of Ser. No. US 1992-958212, filed on 8 Oct 1992, now abandoned
DT Utility
FS Granted
LN.CNT 1544
INCL INCLM: 514/021.000
INCLS: 514/012.000; 435/212.000; 424/529.000; 424/530.000; 424/682.000; 530/381.000; 530/382.000
NCL NCLM: 514/021.000
NCLS: 424/529.000; 424/530.000; 424/682.000; 435/212.000; 514/012.000; 530/381.000; 530/382.000
IC [6]
ICM: A61K038-36
EXF 435/212; 424/529; 424/530; 424/682; 530/381; 530/382; 514/12; 514/21
CAS INDEXING IS AVAILABLE FOR THIS PATENT.

L16 ANSWER 19 OF 25 USPATFULL
AN 1998:51732 USPATFULL
TI Methods and compositions using fibrin monomer to make a fibrin sealant
IN Edwardson, Peter A. D., Chester, United Kingdom
Fairbrother, John E., Clwyd, United Kingdom
Gardner, Ronald S., Clwyd, United Kingdom
Hollingsbee, Derek A., South Wirral, United Kingdom
Cederholm-Williams, Stewart A., Oxford, United Kingdom
PA Bristol-Myers Squibb Company, Skillman, NJ, United States (U.S. corporation)
PI US 5750657 19980512
AI US 1993-138674 19931018 (8)
RLI Continuation-in-part of Ser. No. US 1992-958212, filed on 8 Oct 1992, now abandoned
DT Utility
FS Granted
LN.CNT 1712
INCL INCLM: 530/382.000
INCLS: 530/381.000; 530/383.000; 530/384.000; 435/212.000; 435/214.000; 435/217.000; 424/094.640; 424/529.000; 424/530.000; 514/002.000; 514/008.000; 514/021.000
NCL NCLM: 530/382.000
NCLS: 424/094.640; 424/529.000; 424/530.000; 435/212.000; 435/214.000; 435/217.000; 530/381.000; 530/383.000; 530/384.000
IC [6]
ICM: A61K035-14
ICS: A61K038-36
EXF 435/214; 435/217; 435/212; 424/529; 424/530; 424/94.64; 530/381; 530/382; 530/383; 530/384; 514/2; 514/8; 514/21
CAS INDEXING IS AVAILABLE FOR THIS PATENT.

L16 ANSWER 20 OF 25 USPATFULL
AN 1998:39676 USPATFULL
TI Fibrin sealant compositions

IN Edwardson, Peter A. D., Chester, United Kingdom
Fairbrother, John E., Clwyd, United Kingdom
Gardner, Ronald S., Shotton, United Kingdom
Hollingsbee, Derek A., South Wirral, United Kingdom
Cederholm-Williams, Stewart A., Oxford, United Kingdom
PA Bristol-Myers Squibb Company, Skillman, NJ, United States (U.S. corporation)
PI US 5739288 19980414
AI US 1995-451321 19950526 (8)
RLI Division of Ser. No. US 1993-138674, filed on 18 Oct 1993 which is a continuation-in-part of Ser. No. US 1992-958212, filed on 8 Oct 1992, now abandoned
DT Utility
FS Granted
LN.CNT 1552
INCL INCLM: 530/382.000
INCLS: 530/381.000; 530/380.000; 424/529.000; 424/530.000; 521/012.000; 521/021.000
NCL NCLM: 530/382.000
NCLS: 424/529.000; 424/530.000; 514/012.000; 514/021.000; 530/380.000; 530/381.000
IC [6]
ICM: A61K035-14
EXF 424/529; 424/530; 530/380; 530/381; 530/382; 521/12; 521/21

L16 ANSWER 21 OF 25 USPATFULL
AN 97:16043 USPATFULL
TI Therapeutic fibrinogen compositions
IN Pines, Eli, Watchung, NJ, United States
White, William J., Wayne, PA, United States
PA Fibratek, Inc., Pepper Pike, OH, United States (U.S. corporation)
PI US 5605887 19970225
AI US 1994-225853 19940408 (8)
RLI Division of Ser. No. US 1993-24121, filed on 1 Mar 1993, now patented, Pat. No. US 5330974
DT Utility
FS Granted
LN.CNT 1083
INCL INCLM: 514/021.000
INCLS: 530/382.000; 530/419.000; 530/421.000
NCL NCLM: 514/021.000
NCLS: 530/382.000; 530/419.000; 530/421.000
IC [6]
ICM: A61K038-00
EXF 514/12; 530/382; 530/421; 530/419
CAS INDEXING IS AVAILABLE FOR THIS PATENT.

L16 ANSWER 22 OF 25 USPATFULL
AN 94:62436 USPATFULL
TI Therapeutic fibrinogen compositions
IN Pines, Eli, Watchung, NJ, United States
White, William J., Wayne, PA, United States
PA Fibratek, Inc., Pepper Pike, OH, United States (U.S. corporation)
PI US 5330974 19940719
AI US 1993-24121 19930301 (8)
DT Utility
FS Granted
LN.CNT 1149
INCL INCLM: 514/021.000
INCLS: 530/382.000; 530/419.000; 530/421.000
NCL NCLM: 514/021.000
NCLS: 530/382.000; 530/419.000; 530/421.000
IC [5]
ICM: A61K037-02

ICS: C07K015-08; C07K003-24
EXF 530/382; 530/419; 530/420; 514/21
CAS INDEXING IS AVAILABLE FOR THIS PATENT.

L16 ANSWER 23 OF 25 USPATFULL
AN 89:23206 USPATFULL
TI Method of inactivating reproductive filterable pathogens in fibrinogen and factor XIII compositions
IN Seelich, Thomas, Vienna, Austria
PA Immuno Aktiengesellschaft fur chemisch-medizinische Produkte, Vienna, Austria (non-U.S. corporation)
PI US 4816251 19890328
AI US 1985-775609 19850913 (6)
PRAI AT 1984-3084 19840928
DT Utility
FS Granted
LN.CNT 667
INCL INCLM: 424/101.000
INCLS: 514/002.000; 514/008.000; 530/381.000; 530/382.000
NCL NCLM: 530/382.000
NCLS: 514/002.000; 514/008.000; 530/381.000; 530/383.000
IC [4]
ICM: A61K035-14
EXF 435/236; 424/101; 530/382; 530/383; 514/2; 514/8
CAS INDEXING IS AVAILABLE FOR THIS PATENT.

L16 ANSWER 24 OF 25 USPATFULL
AN 84:20761 USPATFULL
TI Fibrinogen-containing dry preparation, manufacture and use thereof
IN Stroetmann, Michael, Munster, Germany, Federal Republic of
PA Serapharm Michael Stroetmann, Munster, Germany, Federal Republic of (non-U.S. corporation)
PI US 4442655 19840417
AI US 1982-392215 19820625 (6)
PRAI DE 1981-3124962 19810625
DE 1981-3124933 19810625
DE 1981-3131827 19810812
EP 1981-110615 19811218
EP 1982-104606 19820526
DT Utility
FS Granted
LN.CNT 958
INCL INCLM: 053/428.000
INCLS: 106/124.000; 424/101.000; 424/124.000; 424/177.000; 424/359.000; 053/440.000; 424/027.000
NCL NCLM: 053/428.000
NCLS: 053/440.000; 106/124.100; 106/148.100; 424/423.000; 424/445.000; 424/484.000; 424/549.000; 514/773.000; 530/381.000; 623/924.000
IC [3]
ICM: A61K009-14
ICS: A61K035-14; A61K037-00
EXF 424/101; 424/177; 424/27; 424/359; 424/124; 106/124; 053/428
CAS INDEXING IS AVAILABLE FOR THIS PATENT.

L16 ANSWER 25 OF 25 USPATFULL
AN 81:58847 USPATFULL
TI Blood coagulation factors and process for their manufacture
IN Schwinn, Horst, Marburg an der Lahn, Germany, Federal Republic of
Heimburger, Norbert, Marburg an der Lahn, Germany, Federal Republic of
Kumpe, Gerhardt, Wetter, Germany, Federal Republic of
Herchenhan, Bernd, Kirchhain, Germany, Federal Republic of
PA Behringwerke Aktiengesellschaft, Marburg an der Lahn, Germany, Federal Republic of (non-U.S. corporation)
PI US 4297344 19811027

AI US 1980-142962 19800423 (6)
PRAI DE 1979-2916711 19790425
DT Utility
FS Granted
LN.CNT 774
INCL INCLM: 424/101.000
INCLS: 424/176.000; 424/177.000; 260/122.000B
NCL NCLM: 530/381.000
NCLS: 514/822.000; 514/834.000; 530/362.000; 530/380.000; 530/383.000; 530/384.000; 530/393.000; 530/830.000; 530/831.000; 530/851.000
IC [3]
ICM: A61K035-14
ICS: A61K031-00; A61K037-00
EXF 424/101; 424/177; 424/176; 260/112B
CAS INDEXING IS AVAILABLE FOR THIS PATENT.

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L16 ANSWER 1 OF 25 USPATFULL

SUMM [0002] This invention relates generally to storage-stable, concentrated human **fibrinogen** preparations and a method of use therefor to prevent blood loss, to promote **wound** healing, and for many other therapeutic and non-therapeutic applications.

SUMM [0006] Tissue adhesives based on **fibrinogen** are known, for example from U.S. Pat. No. 6,117,425 (MacPhee et al.) In addition to **fibrinogen** and Factor XIII, such formulations may also contain additional proteins, such as fibronectin and albumin, and optionally antibiotic agents, growth factors, and the like. The required catalytic (thrombin-mediated) activity can either originate from the host tissue (the **wound** surface) to which it is applied, or it can be added in the form of a thrombin and Ca.sup.++ ion-containing solution or powder to the tissue adhesive in the course of application. Such fibrin sealants have been used for seamless and/or seam-supporting binding of human or animal tissue or organ parts, for **wound** sealing, hemostasis and promoting **wound** healing, for coating prosthetic devices, and for many other therapeutic and non-therapeutic applications.

SUMM [0007] The **fibrinogen** component of fibrin sealants is derived from pooled human **plasma**, often as a waste product in the **preparation** of human Factor VIII. **Fibrinogen** can be concentrated from human **plasma** by cryoprecipitation, or by **precipitation** by known methods using various reagents, e.g., polyethylene glycol, ether, ethanol, ammonium sulfate or **glycine** . Fibrin sealants are reviewed, for example, by Brennan, Blood Reviews 5:240-244 (1991); Gibble et al., Transfusion 30:741-747 (1990); Matras, J. Oral Maxillofac. Surg. 43:605-611 (1985); Lerner et al., J. Surg. Res. 48:165-181 (1990).

SUMM [0009] At a sufficiently high **fibrinogen** concentration, the preparations provide effective hemostasis, good adherence of the seal to the **wound** and/or tissue areas, high strength of the adhesions and/or **wound** sealings, and complete resorbability of the adhesive in the course of the **wound** healing process. For optimal adhesion, a concentration of **fibrinogen** of about 15 to 60 mg/ml of the ready-to-use tissue adhesive solution is required (MacPhee, personal communication, 1995).

SUMM [0018] An alternative solution to the premature coagulation of the **fibrinogen** solution for use in tissue sealant preparations, U.S. Pat. No. 5,985,315 provides a stable biological pre-activated adhesive comprising **fibrinogen** with the addition of at least one

activated coagulation factor whose activation does not depend on calcium ions. The preactivated adhesive is stable in aqueous solution, i.e., the solution does not coagulate spontaneously for at least one hour at a temperature of 20.degree.; but it can be made to coagulate about 5 minutes simply by adding calcium ions. No additional activator is required. Thus, the resulting biological adhesive requires neither the addition of thrombin or prothrombin to achieve coagulation. Unfortunately, however, such a slow coagulation time would make the use of the resulting fibrin sealant impractical for use on any type of a flowing or pulsating **wound**.

SUMM [0024] The thus prepared and stored, ready-to-use, concentrated human **fibrinogen** solutions may be neutralized and used without additional steps or processes in the preparation of biological tissue adhesives or sealants, including instant fibrin sealant preparations, and for other pharmacologic or cosmetic uses involving, e.g., **wound** healing, coagulation, fibrinogenaemia, inhibition of operative or post-operative sequelae, coating vascular prostheses, or infusion purposes, as well as for other supplemented or unsupplemented therapeutic or non-therapeutic applications in vivo or in vitro.

SUMM [0050] The storage-stable human **fibrinogen** solution of the present invention may be supplemented with, and act as a carrier vehicle for: growth factor(s), drug or other compond(s) or mixtures thereof, so long as noted above, the activity of the **fibrinogen** solution is maintained throughout the length of the storage and spontaneous clotting is not induced. For example, by supplementing the **fibrinogen** preparation with a growth factor, the ready-to-use **fibrinogen** when used to prepare a fibrin sealant or tissue adhesive preparation can accelerate, promote or improve **wound** healing, tissue (re)generation. Such a supplemented preparation may also comprise additional components, e.g., drug(s), antibody(ies), anticoagulant(s) and other compounds that: (1) potentiate, stimulate or mediate the biological activity of the growth factor(s) or other additive(s) or component(s); (2) decrease the activities of one or more additive(s) or component(s) of the growth-factor supplemented human **fibrinogen** or fibrin sealant or tissue adhesive prepared therefrom, wherein such activities would inhibit or destroy the growth factor(s) in the preparation; (3) allow prolonged delivery of the additive or component from a preparation, such as a fibrin sealant or tissue adhesive, made from the ready-to-use **fibrinogen** solution of the present invention; and (4) possess other desirable properties. The contemplated additive(s) or supplement(s) are intended to also include any mutants, derivatives, truncated or other modified forms thereof, which possess similar biological activity(ies), or a subset thereof, to those of the compound or composition from which it is derived.

SUMM [0063] Moreover, the **fibrinogen** preparation and/or the **fibrinogen**-based tissue adhesive to which it is added according to the present invention has no cytotoxic effect when used as a tissue adhesive, i.e., it is "biocompatible," meaning that it is well tolerated by cells, permits a good cell growth and offers an ideal prerequisite for good **wound** healing therewith. This is proven by dilution of the tissue adhesive with the equal volume of the half-isotonic or isotonic sodium chloride solution, and addition to fibroblast growth media. No damaging effect on the fibroblasts is detectable (See Redl et al., 1985).

SUMM [0064] Thus, the present storage-stable, ready-to-use, human **fibrinogen** solutions are prepared in a manner which meets all of the demands of a tissue adhesive, namely biocompatibility, viral safety and high adhesive strength, plus it has the advantage of simple and rapid preparation from the ready-to-use human **fibrinogen**

product. The tissue adhesive prepared from the storage stable human **fibrinogen** of the present invention may be thus used in any known manner in which such biologically-prepared, supplemented or unsupplemented tissue adhesives are used, e.g., pharmacologic or cosmetic uses, including for infusion purposes, such as delivery of antibiotics, antineoplastics, anesthetics, and the like; for **wound** healing, coagulation, and fibrinogenaemia; for inhibition of operative or post-operative sequelae; for coating prostheses; for dressable **wound** sealings and for safe and sustained hemostasis, namely sealing fluid and/or air leakage, and the like in a patient.

PI US 2003091559 A1 20030515

L16 ANSWER 2 OF 25 USPATFULL

SUMM [0002] This invention relates generally to storage-stable, concentrated **fibrinogen** preparations and a method of use therefor to prevent blood loss, to promote **wound** healing, and for many other therapeutic and non-therapeutic applications.

SUMM [0006] Tissue adhesives based on **fibrinogen** are known, for example from U.S. Pat. No. 6,117,425 (MacPhee et al.) In addition to **fibrinogen** and Factor XIII, such formulations may also contain additional proteins, such as fibronectin and albumin, and optionally antibiotic agents, growth factors, and the like. The required catalytic (thrombin-mediated) activity can either originate from the host tissue (the **wound** surface) to which it is applied, or it can be added in the form of a thrombin and Ca.sup.++ ion-containing solution or powder to the tissue adhesive in the course of application. Such fibrin sealants have been used for seamless and/or seam-supporting binding of human or animal tissue or organ parts, for **wound** sealing, hemostasis and promoting **wound** healing, for coating prosthetic devices, and for many other therapeutic and non-therapeutic applications.

SUMM [0007] The **fibrinogen** component of fibrin sealants is derived from pooled blood **plasma**, often as a waste product in the **preparation** of Factor VIII. **Fibrinogen** can be concentrated from **plasma** by cryoprecipitation, or by **precipitation** by known methods using various reagents, e.g., polyethylene glycol, ether, ethanol, ammonium sulfate or **glycine** . Fibrin sealants are reviewed, for example, by Brennan, Blood Reviews 5:240-244 (1991); Gibble et al., Transfusion 30:741-747 (1990); Matras, J. Oral Maxillofac. Surg. 43:605-611 (1985); Lerner et al., J. Surg. Res. 48:165-181 (1990).

SUMM [0009] At a sufficiently high **fibrinogen** concentration, the preparations provide effective hemostasis, good adherence of the seal to the **wound** and/or tissue areas, high strength of the adhesions and/or **wound** sealings, and complete resorbability of the adhesive in the course of the **wound** healing process. For optimal adhesion, a concentration of **fibrinogen** of about 15 to 60 mg/ml of the ready-to-use tissue adhesive solution is required (MacPhee, personal communication, 1995).

SUMM [0018] An alternative solution to the premature coagulation of the **fibrinogen** solution for use in tissue sealant preparations, U.S. Pat. No. 5,985,315 provides a stable biological pre-activated adhesive comprising **fibrinogen** with the addition of at least one activated coagulation factor whose activation does not depend on calcium ions. The preactivated adhesive is stable in aqueous solution, i.e., the solution does not coagulate spontaneously for at least one hour at a temperature of 20.degree.; but it can be made to coagulate about 5 minutes simply by adding calcium ions. No additional activator is

required. Thus, the resulting biological adhesive requires neither the addition of thrombin or prothrombin to achieve coagulation. Unfortunately, however, such a slow coagulation time would make the use of the resulting fibrin sealant impractical for use on any type of a flowing or pulsating **wound**.

SUMM [0025] The thus-prepared and stored, ready-to-use, concentrated mammalian **fibrinogen** solutions may be neutralized and used without additional steps or processes in the preparation of biological tissue adhesives or sealants, including instant fibrin sealant preparations, and for other pharmacologic or cosmetic uses involving, e.g., **wound** healing, coagulation, fibrinogenaemia, inhibition of operative or post-operative sequelae, coating vascular prostheses, or infusion purposes, as well as for other supplemented or unsupplemented therapeutic or non-therapeutic applications in vivo or in vitro.

DETD [0053] The storage-stable **fibrinogen** solution of the present invention may be supplemented with, and act as a carrier vehicle for: growth factor(s), drug or other compond(s) or mixtures thereof, so long as noted above, the activity of the **fibrinogen** solution is maintained throughout the length of the storage and spontaneous clotting is not induced. For example, by supplementing the **fibrinogen** preparation with a growth factor, the ready-to-use **fibrinogen** when used to prepare a fibrin sealant or tissue adhesive preparation can accelerate, promote or improve **wound** healing, tissue (re)generation. Such a supplemented preparation may also comprise additional components, e.g., drug(s), antibody(ies), anticoagulant(s) and other compounds that: (1) potentiate, stimulate or mediate the biological activity of the growth factor(s) or other additive(s) or component(s); (2) decrease the activities of one or more additive(s) or component(s) of the growth-factor supplemented **fibrinogen** or fibrin sealant or tissue adhesive prepared therefrom, wherein such activities would inhibit or destroy the growth factor(s) in the preparation; (3) allow prolonged delivery of the additive or component from a preparation, such as a fibrin sealant or tissue adhesive, made from the ready-to-use **fibrinogen** solution of the present invention; and (4) possess other desirable properties. The contemplated additive(s) or supplement(s) are intended to also include any mutants, derivatives, truncated or other modified forms thereof, which possess similar biological activity(ies), or a subset thereof, to those of the compound or composition from which it is derived.

DETD [0066] Moreover, the **fibrinogen** preparation and/or the **fibrinogen**-based tissue adhesive to which it is added according to the present invention has no cytotoxic effect when used as a tissue adhesive, i.e., it is "biocompatible," meaning that it is well tolerated by cells, permits a good cell growth and offers an ideal prerequisite for good **wound** healing therewith. This is proven by dilution of the tissue adhesive with the equal volume of the half-isotonic or isotonic sodium chloride solution, and addition to fibroblast growth media. No damaging effect on the fibroblasts is detectable (See Redl et al., 1985).

DETD [0067] Thus, the present storage-stable, ready-to-use **fibrinogen** solutions are prepared in a manner which meets all of the demands of a tissue adhesive, namely biocompatibility, viral safety and high adhesive strength, plus it has the advantage of simple and rapid preparation from a ready-to-use **fibrinogen** product. The tissue adhesive prepared from the storage stable **fibrinogen** of the present invention may be thus used in any known manner in which such biologically-prepared, supplemented or unsupplemented tissue adhesives are used, e.g., pharmacologic or cosmetic uses, including for infusion purposes, such as delivery of antibiotics, antineoplastics, anesthetics, and the like; for **wound** healing, coagulation, and fibrinogenaemia; for inhibition of operative or post-operative sequelae; for coating prostheses; for dressable **wound** sealings and for

safe and sustained hemostasis, namely sealing fluid and/or air leakage, and the like in a patient.

PI US 2003091558 A1 20030515

L16 ANSWER 3 OF 25 USPATFULL

SUMM [0002] Tissue adhesives based on **fibrinogen** ("fibrin adhesives") have been known for a long time. They serve for a seamless or suture-supporting connection of human or animal tissues or organ parts, for sealing **wounds**, haemostasis and assisting **wound** healing.

SUMM [0004] By the action of thrombin, (soluble) **fibrinogen** at first is converted into fibrin monomers which aggregate spontaneously and form a sticky mass, a so-called fibrin clot. Simultaneously, factor XIII (F XIII) present is activated by thrombin in the presence of calcium ions to factor XIIIa. By the latter, the aggregated fibrin monomers and also fibronectin possibly present are cross-linked to a high polymer by new peptide bonds forming. By this cross-linking reaction, the strength of the clot formed is substantially increased. Generally, the clot adheres well to **wound** and tissue surfaces, which i. a. leads to the adhesive and haemostatic effect.

SUMM [0016] Methods for producing **fibrinogen**-containing **preparations** which can be used as tissue adhesives comprise i.a. their production from cryoprecipitate, optionally with further washing and **precipitation** steps with ethanol, ammonium sulphate, polyethylene glycol, **glycine** or .beta.-alanine, and their production from **plasma** within the scope of the known **plasma** fractionation methods, respectively (cf., e.g., "Methods of **plasma** protein fractionation", 1980, ed.: Curling, Academic Press, pp. 3-15, 33-36 and 57-74, or Blomb{overscore (a)}ck B. and M., "Purification of human and bovine **fibrinogen**", Arkiv Kemi 10, 1959, p. 415 f.).

PI US 2003077270 A1 20030424

L16 ANSWER 4 OF 25 USPATFULL

SUMM [0016] In **wound** healing, the final stage of the coagulation cascade results in the formation of insoluble fibrin, which forms the insoluble structure of the blood clot. The fibrin is formed from **fibrinogen** in the presence of other plasma components, most notably, thrombin and factor XIII, wherein the thrombin converts **fibrinogen** and factor XIII into their reactive forms.

SUMM [0032] Fibrin glue is composed of a mixture of human **fibrinogen** and bovine thrombin. It is sold as a kit containing separate vials of **fibrinogen** and thrombin solutions. These solutions are mixed together and applied to the **wound** in various ways, including as a paste, as a spray or on a patch. Fibrin glue, however, is an inconsistent and ineffective therapy for hemostasis. The mixing, soaking, and coating of a patch with fibrin glue requires time-consuming and cumbersome procedures. Each of the preparation steps introduces potential errors and thus their efficacy varies with the experience of operating room personnel. Moreover, during the preparation of such solution, further hemorrhage occurs and the solutions are washed away by intense bleeding. Despite the headway made in **fibrinogen** compositions and surgical techniques, these pitfalls in achieving hemostasis underscore the need for development of a suitable product.

SUMM [0038] In addition, the **fibrinogen** for use in the above fibrin glue is often concentrated from human **plasma** by cryoprecipitation and **precipitation** using various reagents, e.g., polyethylene glycol, ether, ethanol, ammonium sulfate or **glycine**. There always exists the risk of an immunogenic reaction

to the **fibrinogen** component of traditional fibrin glue **preparations**.

SUMM [0044] U.S. Pat. No. 5,330,974 advocates a tissue adhesive which contains **fibrinogen**, factor XIII, a thrombin inhibitor, prothrombin factors, calcium ions and, where appropriate, a plasmin inhibitor. The object of this invention disclosed therein lies in applying the tissue adhesive to the **wound** site, wherein the components of the tissue adhesive acting in concert with accelerators which are naturally present on the **wound** which is to be bonded result in the thrombin which is necessary for adhesion being liberated from the prothrombin in the adhesive. Practice of this patented invention however, requires the combination of the above reference components.

SUMM [0060] As such, the above voids in the prior art have created an urgent need for a suitable hemostatic polymer composition which not only induces rapid blood coagulation and hemostasis at a **wound** or bleeding site, but also does away for the need of exogenous thrombin because of its ability to concentrate the patients own **fibrinogen**, which in turn, greatly facilitates the formation of a clot.

DETD [0104] The present invention is based upon the discovery that the homeostatic polymer composition is able to induce rapid blood clotting by concentrating the patients **fibrinogen** in vivo at the site of the **wound** or bleeding site. The hemostatic polymer composition, acting in concert with the concentrated **fibrinogen** activates the patients platelets and RBC's to convert prothrombin to thrombin without the addition of exogenous thrombin. See FIG. 11. It is understood that the use of the hemostatic polymer composition is not intended to be limited to the examples appearing here below. Indeed, the hemostatic polymer composition is useful for rapid blood coagulation in all mammals, including humans

DETD [0123] Briefly, the hemostatic polymer composition is the product of a polymerization process which ultimately results in the formation of an insoluble, three-dimensional cross-linked polymer network. The resulting three-dimensional network of cross-linked polymer that defines the polymer bead or grains of the hemostatic polymer composition of the invention is formed by reacting an uncharged organic substance, containing hydroxyl group reaction sites, with either halogen or epoxy groups of a bifunctional organic substance. The three-dimensional network of cross-linked polymer may take the shape of a gel, sphere, fiber, mesh or netting when it is applied to the **wound** or bleeding site. A distinct feature of the bead is the presence of a three-dimensional hemostatic cascade reaction zone. The three-dimensional polymer network is further characterized as being devoid of ionized groups, insoluble in the solvent but capable of swelling in the solvent. In addition, the polymer bead of the hemostatic polymer composition is inert with regard to the substance to be isolated in-vivo i.e.--**fibrinogen**.

DETD [0125] Without being limited as to theory, it is likely that hemostasis occurs at the site of bleeding by the concentration of plasma proteins (i.e. **fibrinogen** and other clotting factors). At the start of the hemostatic cascade reaction process, depending upon the molecular dimension of the protein and the size of the pores in the three-dimensional polymer network that defines the beads of the homeostatic composition, the beads upon absorbing water, saline, plasma etc. absorb low molecular weight plasma components at the surface of the polymer beads (first layer) while concentrating higher molecular weight plasma proteins and **fibrinogen** just outside the first layer. The concentrated **fibrinogen**, in turn, forms a matrix of clotting factors, both low molecular weight and high molecular clotting factors that essentially surround the beads of the composition and also

fill the interstitial space between the bead and the **wound** site as well as the spaces between the beads. It should be noted that beads closest to the **wound** site form matrixes before those farther way, and generally form the clotting matrixes as they come in contact with the blood.

DETD [0140] Thus, upon contacting a **wound** or bleeding site, the less-hydrated or dry beads of the hemostatic polymer composition effectively concentrate low molecular weight plasma components, those defined by a molecular weight of less than 300,000 (<300,000 MW), and higher molecular weight plasma components, those defined by a molecular weight of more than 300,000 (>300,000 MW) such as **fibrinogen** and effectively form a three-dimensional clotting matrix that essentially surrounds the beads of the composition. See FIG. 11 for example.

DETD [0241] The object of this experiment was to compare the ability of conventional Avitene, Cochrum Fibrin Glue (U.S. Pat. No. 5,510,102) and the dry hemostatic polymer composition of the invention. Two liver incisions 4 cm.times.2 cm were sealed with Avitene (very poor results). Two liver incisions were sealed with Cochrum Fibrin Glue (U.S. Pat. No. 5,510,102). Although the Cochrum Fibrin Glue adhered the incision better than Avitene, the fibrin glue (plasma/polymer) however, unable to maintain hemostasis in **wounds** that bled profusely (arterial bleeding). The Fibrin Glue tended to stop the bleeding (due to the concentrated **fibrinogen** and Bovine Thrombin), however the hemostasis could not be maintained under arterial pressure.

PI US 2002197302 A1 20021226

L16 ANSWER 5 OF 25 USPATFULL

SUMM [0002] Tissue adhesives based on **fibrinogen** ("fibrin adhesives") have been known for a long time. They serve for a seamless or suture-supporting connection of human or animal tissues or organ parts, for sealing **wounds**, haemostasis and assisting **wound** healing.

SUMM [0004] By the action of thrombin, (soluble) **fibrinogen** at first is converted into fibrin monomers which aggregate spontaneously and form a sticky mass, a so-called fibrin clot. Simultaneously, factor XIII (F XIII) present is activated by thrombin in the presence of calcium ions to factor XIIIa. By the latter, the aggregated fibrin monomers and also fibronectin possibly present are cross-linked to a high polymer by new peptide bonds forming. By this cross-linking reaction, the strength of the clot formed is substantially increased. Generally, the clot adheres well to **wound** and tissue surfaces, which i. a. leads to the adhesive and haemostatic effect.

SUMM [0016] Methods for producing **fibrinogen**-containing **preparations** which can be used as tissue adhesives comprise i. a. their production from cryoprecipitate, optionally with further washing and **precipitation** steps with ethanol, ammonium sulphate, polyethylene glycol, **glycine** or .beta.-alanine, and their production from **plasma** within the scope of the known **plasma** fractionation methods, respectively (cf., e.g., "Methods of **plasma** protein fractionation", 1980, ed.: Curling, Academic Press, pp. 3-15, 33-36 and 57-74, or Blomb{overscore (a)}ck B. and M., "purification of human and bovine **fibrinogen**", Arkiv Kemi 10, 1959, p. 415 f.).

PI US 2002172718 A1 20021121

L16 ANSWER 6 OF 25 USPATFULL

AB The invention relates to a medicament for topical application for the purpose of stopping bleeding and/or closing **wounds** and/or promoting **wound** healing, which as active substances --produced conventionally of allogenic plasma or tissue or recombinantly--contains

fibrinogen or fibrin, thrombin and one or several tranglutaminase(s), wherein the medicament, as a further active substance, contains one or several protease inhibitor(s) selected from the group consisting of serpins that do not have inhibiting effects on collagenases and elastases, all of the active substances being of allogenic origin and having been subjected to a process for virus depletion and/or virus inactivation, with the proviso that the virus inactivtion of the one or several protease inhibitor(s) has not been carried out in the presence of the other active substances.

SUMM [0005] The use of enriched **fibrinogen** solutions instead of plasma for the purpose of stopping bleeding and closing **wounds** in the beginning likewise was unsuccessful, but finally a substantial success could be achieved by raising the **fibrinogen** concentration of such **fibrinogen**-containing solutions to more than ten times the **fibrinogen** level in plasma (Loblich, 1975, unpublished communication).

SUMM [0006] When converting **fibrinogen** into fibrin, it may happen that the hemostatically effective fibrin **wound** closure will be detached by **wound** bed enzymes after some hours, thereby causing afterbleeding. The detachment of the fibrin **wound** closure from the **wound** bed is a substantially more frequent and hence more dangerous procedure than the fibrinolysis of the whole fibrin **wound** closure.

SUMM [0007] It was proved already by the first successful applications of highly concentrated **fibrinogen** solutions (Matras, H. et al., 1972, Wr. Med. Wschr. 122:517-523) and the conversion of **fibrinogen** to fibrin by thrombin in the **wound** area that any detachment of the fibrin **wound** closure and the usually involved afterbleedings could be avoided by means of fibrinolysis inhibitors. Among the low-molecular inhibitors assayed, epsilon-aminocaproic acid and derivatives could be proved effective, yet they had the disadvantage of rapidly diffunding out of the coagulated fibrin and of the **wound** area, and hence losing their topical efficacy.

SUMM [0010] Another difficulty in producing pharmaceutical medicaments containing **fibrinogen** and thrombin as well as an allogenic protease inhibitor and a transglutaminase zymogen is due to the virus inactivation of such preparations, which has been required for quite some time. A large portion of the activity of the protease inhibitor or transglutaminase zymogen respectively contained in the preparation will be lost by virus inactivation in most cases such that the preparations obtained after having carried out the virus inactivation process frequently will exhibit but a low activity of the protease inhibitor or transglutarninase zymogen, respectively. This may result in an insufficient inhibition of fibrinolytic enzymes present in the **wound** bed and, consequently, in the detachment of the fibrin **wound** closure from the **wound** bed.

SUMM [0040] Concentrated **fibrinogen** solutions involve a number of drawbacks. They offer reduced storage stability and must be deepfrozen or freeze-dried for storage and cannot always be made usable or reconstituted in a satisfactory manner by thawing or redissolving. Moreover, the dissolution of a **fibrinogen** lyophilisate requires some time. Solubilizers or readily soluble **fibrinogens**, in most cases, are cytotoxic and, therefore, not suitable for an undisturbed **wound** healing.

DETD [0063] The **plasma** as such, the Cohn fraction I and the cryoprecipitate after dissolution in about 20 liters of 0.9% NaCl and 0.1% sodium citrate buffer pH 7, are supplemented to saturation with solid **glycine** having a degree of purity suitable for

pharmaceutical **preparations** while being cooled to -2.degree. C. to -3.degree. C., stored at that temperature for a minimum of 10 to a maximum of 15 hours, separated from undissolved **glycine**, and the **fibrinogen**-fibronectin-containing **precipitate** is separated by centrifugation in a high-speed centrifuge.

CLM What is claimed is:

1. A topical medicament intended for stopping bleeding, closing a **wound**, or promoting **wound** healing in a subject in need of such treatment, comprising the following active agents in therapeutic amounts: (i) an agent selected from the group consisting of **fibrinogen** and fibrin; (ii) thrombin; (iii) a transglutaminase; and (iv) a serpin protease inhibitor which does not inhibit collagenase and elastase; wherein the active agents may be obtained from a source selected from the group of allogenic plasma, allogenic tissue, and recombinant production; and wherein an active substance of allogenic origin is subjected to a process selected from the group consisting of virus depletion, virus inactivation and a combination thereof; provided that where such a process is applied to the serpin protease inhibitor, it is not applied in the presence of one or more of the other active agents

121. A method of treating a **wound** of a subject, comprising applying, to the **wound**, a topical medicament comprising the following active agents in therapeutic amounts: (i) an agent selected from the group consisting of **fibrinogen** and fibrin; (ii) thrombin; (iii) a transglutaminase; and (iv) a serpin protease inhibitor which does not inhibit collagenase and elastase; wherein the active agents may be obtained from a source selected from the group of allogenic plasma, allogenic tissue, and recombinant production; and wherein an active substance of allogenic origin is subjected to a process selected from the group consisting of virus depletion, virus inactivation and a combination thereof; provided that where such a process is applied to the serpin protease inhibitor, it is not applied in the presence of one or more of the other active agents.

PI US 2002114796 A1 20020822

L16 ANSWER 7 OF 25 USPATFULL

SUMM [0013] The importance of A.alpha. C-terminal regions to **fibrinogen** properties has inspired the development of techniques whereby **fibrinogen** molecules having varying degrees of A.alpha. chain proteolysis can be separated for study. Various methods have been described for the separation of the major **fibrinogen** sub-families and FDPs. For example **precipitation** techniques have been used to separate F1 and F2 from purified **fibrinogen** [Sasaki and Kito, Simplified determination of **fibrinogen** sub-fractions by **glycine precipitation**, Thrombosis and Haemostasis 42:440-443, 1979]. Holm et al., have described a method for the separation of purified **plasma fibrinogen** into F1, F2 & F3 subfamilies by using a series of **precipitations** with ammonium sulphate. F3. fragments Y, D and E have been separated based on size using size exclusion chromatography [Morder and Raphael Shulman, High molecular weight derivatives of human **fibrinogen** produced by plasmin, Journal of Biological Chemistry, 244:2120-2124, 1969]. These authors also demonstrated that F3 **fibrinogen** and FDPs Y, D and E actually possess anticoagulant activity and are inhibitory to clot formation; a non-desirable feature of a molecule used to **prepare** a surgical adhesive. Most attention has been paid to the terminal degradation products D and E which have been separated using anion exchange chromatography [Kemp et al., Plasmic degradation of **fibrinogen**: the **preparation** of a low molecular weight derivative of fragment D,

SUMM [0103] While the main use of **fibrinogen** is thought to be for

the preparation of adhesive or sealing agents as hereinbefore described, **fibrinogen** has other applications in the field of medicine, for example as a coating for polymeric articles as disclosed in U.S. Pat. No. 5,272,074. A particular use of lyophilised **fibrinogen** of the present invention is within or part of a gauze or bandage (preferably made from polylactic acid compounds used in surgical stitches). Such a **wound** dressing can be supplied (also incorporating the other components required for the formation of a clot (described above), optionally in a package or kit form, for application direct to the skin or to an internal organ. All details and features of previously discussed aspects, also apply to the twelfth.

PI US 2002019025 A1 20020214

L16 ANSWER 8 OF 25 USPATFULL

SUMM The **fibrinogen** component of the fibrin sealant is **prepared** from pooled human **plasma**. The **fibrinogen** can be concentrated from the human **plasma** by cryoprecipitation and **precipitation** using various reagents, e.g., polyethylene glycol, ether, ethanol, ammonium sulfate or **glycine**. For an excellent review of fibrin sealants, see M. Brennan, Blood Reviews, 5:240-244 (1991); J. W. Gibble and P. M. Ness, Transfusion, 30:741-747 (1990); H. Matras, J. Oral Maxillofac Surg., 43:605-611 (1985) and R. Lerner and N. Binur, J. of Surgical Research, 48:165-181 (1990).

SUMM Fibrin I monomer is preferred because it can, in contrast to **fibrinogen**, readily be converted to fibrin polymer without the use of thrombin or factor XIII. In fact, the fibrin I monomer can spontaneously form fibrin I polymer, which can act as the fibrin clot, regardless of whether the fibrin I polymer is crosslinked or noncrosslinked or further converted to fibrin II polymer. Thus, since the formation of the fibrin I polymer from fibrin I monomer is spontaneous, the fibrin I polymer can be formed without thrombin and factor XIII, thereby avoiding the problems associated with bovine thrombin. (It should be noted that if fibrin I monomer is utilized such that the fibrin I monomer comes into contact with patient's blood, for example, on a **wound**, the patient's thrombin and factor XIII may convert the fibrin I polymer to crosslinked fibrin II polymer.)

SUMM Noncrosslinked fibrin I is preferred because it can more readily, as compared to **fibrinogen**, be converted to crosslinked fibrin. In fact, it is believed that fibrin I can form crosslinked fibrin I, which can act as the fibrin sealant. Thus, the formation of the crosslinked fibrin I from noncrosslinked fibrin I can be carried out without thrombin, thereby avoiding the problems associated with bovine thrombin, albeit activated factor XIII may be required. (It should be noted that if noncrosslinked fibrin I is utilized such that the noncrosslinked fibrin I comes into contact with patient's blood, for example, on a **wound**, the patient's thrombin and factor XIII may convert the fibrin I to crosslinked fibrin II.)

PI US 6262236 B1 20010717

L16 ANSWER 9 OF 25 USPATFULL

SUMM The **fibrinogen** component of the fibrin sealant is **prepared** from pooled human **plasma**. The **fibrinogen** can be concentrated from the human **plasma** by cryoprecipitation and **precipitation** using various reagents, e.g., polyethylene glycol, ether, ethanol, ammonium sulfate or **glycine**. For an excellent review of fibrin sealants, see M. Brennan, Blood Reviews, 5:240-244 (1991); J. W. Gibble and P. M. Ness, Transfusion, 30:741-747 (1990); H. Matras, J. Oral Maxillofac Sura., 43:605-611 (1985) and R. Lerner and N. Binur, J. of Surgical Research,

48:165-181 (1990).

DETD Fibrin I monomer is preferred because it can, in contrast to **fibrinogen**, readily be converted to fibrin polymer without the use of thrombin or factor XIII. In fact, the fibrin I monomer can spontaneously form fibrin I polymer, which can act as the fibrin clot, regardless of whether the fibrin I polymer is crosslinked or noncrosslinked or further converted to fibrin II polymer. Thus, since the formation of the fibrin I polymer from fibrin I monomer is spontaneous, the fibrin I polymer can be formed without thrombin and factor XIII, thereby avoiding the problems associated with bovine thrombin. (It should be noted that if fibrin I monomer is utilized such that the fibrin I monomer comes into contact with patient's blood, for example, on a **wound**, the patient's thrombin and factor XIII may convert the fibrin I polymer to crosslinked fibrin II polymer.)

DETD Noncrosslinked fibrin I is preferred because it can more readily, as compared to **fibrinogen**, be converted to crosslinked fibrin. In fact, it is believed that fibrin I can form crosslinked fibrin I, which can act as the fibrin sealant. Thus, the formation of the crosslinked fibrin I from noncrosslinked fibrin I can be carried out without thrombin, thereby avoiding the problems associated with bovine thrombin, albeit activated factor XIII may be required. (It should be noted that if noncrosslinked fibrin I is utilized such that the noncrosslinked fibrin I comes into contact with patient's blood, for example, on a **wound**, the patient's thrombin and factor XIII may convert the fibrin I to crosslinked fibrin II.)

PI US 6077507 20000620

L16 ANSWER 10 OF 25 USPATFULL

SUMM The **fibrinogen** component of the fibrin sealant is **prepared** from pooled human **plasma**. The **fibrinogen** can be concentrated from the human **plasma** by cryoprecipitation and **precipitation** using various reagents, e.g., polyethylene glycol, ether, ethanol, ammonium sulfate or **glycine**. For an excellent review of fibrin sealants, see M. Brennan, Blood Reviews, 5:240-244 (1991); J. W. Gibble and P. M. Ness, Transfusion, 30:741-747 (1990); H. Matras, J. Oral Maxillofac Surg., 43:605-611 (1985) and R. Lerner and N. Binur, J. of Surgical Research, 48:165-181 (1990).

DETD Fibrin I monomer is preferred because it can, in contrast to **fibrinogen**, readily be converted to fibrin polymer without the use of thrombin or factor XIII. In fact, the fibrin I monomer can spontaneously form fibrin I polymer, which can act as the fibrin clot, regardless of whether the fibrin I polymer is crosslinked or noncrosslinked or further converted to fibrin II polymer. Thus, since the formation of the fibrin I polymer from fibrin I monomer is spontaneous, the fibrin I polymer can be formed without thrombin and factor XIII, thereby avoiding the problems associated with bovine thrombin. (It should be noted that if fibrin I monomer is utilized such that the fibrin I monomer comes into contact with patient's blood, for example, on a **wound**, the patient's thrombin and factor XIII may convert the fibrin I polymer to crosslinked fibrin II polymer.)

DETD Noncrosslinked fibrin I is preferred because it can more readily, as compared to **fibrinogen**, be converted to crosslinked fibrin. In fact, it is believed that fibrin I can form crosslinked fibrin I, which can act as the fibrin sealant. Thus, the formation of the crosslinked fibrin I from noncrosslinked fibrin I can be carried out without thrombin, thereby avoiding the problems associated with bovine thrombin, albeit activated factor XIII may be required. (It should be noted that if noncrosslinked fibrin I is utilized such that the noncrosslinked fibrin I comes into contact with patient's blood, for example, on a **wound**, the patient's thrombin and factor XIII may convert the fibrin I to crosslinked fibrin II.)

PI US 6048966 20000411

L16 ANSWER 11 OF 25 USPATFULL
SUMM The **fibrinogen** component of the fibrin sealant is **prepared** from pooled human **plasma**. The **fibrinogen** can be concentrated from the human **plasma** by cryoprecipitation and **precipitation** using various reagents, e.g., polyethylene glycol, ether, ethanol, ammonium sulfate or **glycine**. For an excellent review of fibrin sealants, see M. Brennan, Blood Reviews, 5:240-244 (1991); J. W. Gibble and P. M. Ness, Transfusion, 30:741-747 (1990); H. Matras, J. Oral Maxillofac Surg., 43:605-611 (1985) and R. Lerner and N. Binur, J. of Surgical Research, 48:165-181 (1990).

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DETD Noncrosslinked fibrin I is preferred because it can more readily, as compared to **fibrinogen**, be converted to crosslinked fibrin. In fact, it is believed that fibrin I can form crosslinked fibrin I, which can act as the fibrin sealant. Thus, the formation of the crosslinked fibrin I from noncrosslinked fibrin I can be carried out without thrombin, thereby avoiding the problems associated with bovine thrombin, albeit activated factor XIII may be required. (It should be noted that if noncrosslinked fibrin I is utilized such that the noncrosslinked fibrin I comes into contact with patient's blood, for example, on a **wound**, the patient's thrombin and factor XIII may convert the fibrin I to crosslinked fibrin II.)
PI US 5962420 19991005

L16 ANSWER 12 OF 25 USPATFULL
SUMM Tissue adhesives based on **fibrinogen** are employed for seamless and/or seam-supporting binding of human or animal tissue or organ parts, for **wound** sealing, hemostasis and promoting **wound** healing.

SUMM Their mode of action is based on the fact that the (soluble) **fibrinogen** contained in a ready-to-use, liquid tissue adhesive is converted into (insoluble) fibrin and the Factor XIII also contained therein is activated to Factor XIIIa, by the action of thrombin. This crosslinks the formed fibrin to a high polymer which is essential for the effectiveness of the tissue adhesive. The required thrombin activity can either originate from the tissue (the **wound** surface) to be adhered or can be added in the form of a thrombin and Ca.sup.2+ ion-containing solution to the tissue adhesive in the course of the sealing. Tissue adhesives based on **fibrinogen** are already known from AT-B-359 653, AT-B-359 652 and AT-B-369 990. Aside from **fibrinogen** and Factor XIII they also contain further proteins such as fibronectin and albumin and optionally antibiotic agents. Tissue adhesives are marketed either in the form of deep-frozen solutions or as a lyophilisate because as a liquid solution they are not very stable over a longer period of time. These circumstances lead to the fact that the commercial products must be either thawed, i.e. liquefied, or reconstituted from their lyophilisate before their application. Both

measures are associated with significant efforts.

SUMM EP-A-085 923 describes a lyophilized **fibrinogen** preparation which, aside from **fibrinogen**, further contains a substance which possesses an urea or a guanidine group. However, it has been demonstrated that lyophilized tissue adhesive preparations made accordingly act cytotoxically, inhibit the growth of fibroblasts and lead to an altered, nonphysiological fibrin structure whereby the desired elasticity of fibrin and the seal is lost (see Redl et al., Medizinische Welt 36, 769-76 (1985)). By the inhibition of the fibroblast growth, i.e. those cells which initiate the **wound** healing process, the desired **wound** healing promoting properties of tissue adhesives based on **fibrinogen** are lost. Further, the required high adhesive strength in vivo is jeopardized by the absent elasticity of the resulting fibrin.

DETD A purified lyophilized **fibrinogen preparation** (bulk material) was essentially produced according to L. A. Kazal et al., Proc. Soc. Exp. Biol. Med. 113, 989-994, 1963, by **glycine precipitation** from a **fibrinogen**-containing human **plasma** fraction.

PI US 5962405 19991005

L16 ANSWER 13 OF 25 USPATFULL

SUMM The **fibrinogen** component of the fibrin sealant is **prepared** from pooled human **plasma**. The **fibrinogen** can be concentrated from the human **plasma** by cryoprecipitation and **precipitation** using various reagents, e.g., polyethylene glycol, ether, ethanol, ammonium sulfate or **glycine**. For an excellent review of fibrin sealants, see M. Brennan, Blood Reviews, 5:240-244 (1991); J. W. Gibble and P. M. Ness, Transfusion, 30:741-747 (1990); H. Matras, J. Oral Maxillofac Surg., 43:605-611 (1985) and R. Lerner and N. Binur, J. of Surgical Research, 48:165-181 (1990).

DETD Fibrin I monomer is preferred because it can, in contrast to **fibrinogen**, readily be converted to fibrin polymer without the use of thrombin or factor XIII. In fact, the fibrin I monomer can spontaneously form fibrin I polymer, which can act as the fibrin clot, regardless of whether the fibrin I polymer is crosslinked or noncrosslinked or further converted to fibrin II polymer. Thus, since the formation of the fibrin I polymer from fibrin I monomer is spontaneous, the fibrin I polymer can be formed without thrombin and factor XIII, thereby avoiding the problems associated with bovine thrombin. (It should be noted that if fibrin I monomer is utilized such that the fibrin I monomer comes into contact with patient's blood, for example, on a **wound**, the patient's thrombin and factor XIII may convert the fibrin I polymer to crosslinked fibrin II polymer.)

DETD Noncrosslinked fibrin I is preferred because it can more readily, as compared to **fibrinogen**, be converted to crosslinked fibrin. In fact, it is believed that fibrin I can form crosslinked fibrin I, which can act as the fibrin sealant. Thus, the formation of the crosslinked fibrin I from noncrosslinked fibrin I can be carried out without thrombin, thereby avoiding the problems associated with bovine thrombin, albeit activated factor XIII may be required. (It should be noted that if noncrosslinked fibrin I is utilized such that the noncrosslinked fibrin I comes into contact with patient's blood, for example, on a **wound**, the patient's thrombin and factor XIII may convert the fibrin I to crosslinked fibrin II.)

PI US 5962026 19991005

L16 ANSWER 14 OF 25 USPATFULL

SUMM The **fibrinogen** component of the fibrin sealant is **prepared** from pooled human **plasma**. The

fibrinogen can be concentrated from the human **plasma** by cryoprecipitation and **precipitation** using various reagents, e.g., polyethylene glycol, ether, ethanol, ammonium sulfate or **glycine**. For an excellent review of fibrin sealants, see M. Brennan, Blood Reviews, 5:240-244 (1991); J. W. Gibble and P. M. Ness, Transfusion, 30:741-747 (1990); H. Matras, J. Oral Maxillofac Surg., 43:605-611 (1985) and R. Lerner and N. Binur, J. of Surgical Research, 48:165-181 (1990).

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SUMM Noncrosslinked fibrin I is preferred because it can more readily, as compared to **fibrinogen**, be converted to crosslinked fibrin. In fact, it is believed that fibrin I can form crosslinked fibrin I, which can act as the fibrin sealant. Thus, the formation of the crosslinked fibrin I from noncrosslinked fibrin I can be carried out without thrombin, thereby avoiding the problems associated with bovine thrombin, albeit activated factor XIII may be required. (It should be noted that if noncrosslinked fibrin I is utilized such that the noncrosslinked fibrin I comes into contact with patient's blood, for example, on a **wound**, the patient's thrombin and factor XIII may convert the fibrin I to crosslinked fibrin II.)

PI US 5804428 19980908

L16 ANSWER 15 OF 25 USPATFULL

SUMM The **fibrinogen** component of the fibrin sealant is **prepared** from pooled human **plasma**. The **fibrinogen** can be concentrated from the human **plasma** by cryoprecipitation and **precipitation** using various reagents, e.g., polyethylene glycol, ether, ethanol, ammonium sulfate or **glycine**. For an excellent review of fibrin sealants, see M. Brennan, Blood Reviews, 5:240-244 (1991); J. W. Gibble and P. M. Ness, Transfusion, 30:741-747 (1990); H. Matras, J. Oral Maxillofac surg., 43:605-611 (1985) and R. Lerner and N. Binur, J. of Surgical Research, 48:165-181 (1990).

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DETD Noncrosslinked fibrin I is preferred because it can more readily, as compared to **fibrinogen**, be converted to crosslinked fibrin. In

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PI US 5773418 19980630

L16 ANSWER 16 OF 25 USPATFULL

SUMM The **fibrinogen** component of the fibrin sealant is **prepared** from pooled human **plasma**. The **fibrinogen** can be concentrated from the human **plasma** by cryoprecipitation and **precipitation** using various reagents, e.g., polyethylene glycol, ether, ethanol, ammonium sulfate or **glycine**. For an excellent review of fibrin sealants, see M. Brennan, Blood Reviews, 5:240-244 (1991); J. W. Gibble and P. M. Ness, Transfusion, 30:741-747 (1990); H. Matras, J. Oral Maxillofac Sura., 43:605-611 (1985) and R. Lerner and N. Binur, J. of Surgical Research, 48:165-181 (1990).

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DETD Noncrosslinked fibrin I is preferred because it can more readily, as compared to **fibrinogen**, be converted to crosslinked fibrin. In fact, it is believed that fibrin I can form crosslinked fibrin I, which can act as the fibrin sealant. Thus, the formation of the crosslinked fibrin I from noncrosslinked fibrin I can be carried out without thrombin, thereby avoiding the problems associated with bovine thrombin, albeit activated factor XIII may be required. (It should be noted that if noncrosslinked fibrin I is utilized such that the noncrosslinked fibrin I comes into contact with patient's blood, for example, on a **wound**, the patient's thrombin and factor XIII may convert the fibrin I to crosslinked fibrin II.)

PI US 5770194 19980623

L16 ANSWER 17 OF 25 USPATFULL

SUMM The **fibrinogen** component of the fibrin sealant is **prepared** from pooled human **plasma**. The **fibrinogen** can be concentrated from the human **plasma** by cryoprecipitation and **precipitation** using various reagents, e.g., polyethylene glycol, ether, ethanol, ammonium sulfate or **glycine**. For an excellent review of fibrin sealants, see M. Brennan, Blood Reviews, 5:240-244 (1991); J. W. Gibble and P. M. Ness, Transfusion, 30:741-747 (1990); H. Matras, J. Oral Maxillofac Surg., 43:605-611 (1985) and R. Lerner and N. Binur, J. of Surgical Research, 48:165-181 (1990).

SUMM Fibrin I monomer is preferred because it can, in contrast to **fibrinogen**, readily be converted to fibrin polymer without the use of thrombin or factor XIII. In fact, the fibrin I monomer can

spontaneously form fibrin I polymer, which can act as the fibrin clot, regardless of whether the fibrin I polymer is crosslinked or noncrosslinked or further converted to fibrin II polymer. Thus, since the formation of the fibrin I polymer from fibrin I monomer is spontaneous, the fibrin I polymer can be formed without thrombin and factor XIII, thereby avoiding the problems associated with bovine thrombin. (It should be noted that if fibrin I monomer is utilized such that the fibrin I monomer comes into contact with patient's blood, for example, on a **wound**, the patient's thrombin and factor XIII may convert the fibrin I polymer to crosslinked fibrin II polymer.)

SUMM Noncrosslinked fibrin I is preferred because it can more readily, as compared to **fibrinogen**, be converted to crosslinked fibrin. In fact, it is believed that fibrin I can form crosslinked fibrin I, which can act as the fibrin sealant. Thus, the formation of the crosslinked fibrin I from noncrosslinked fibrin I can be carried out without thrombin, thereby avoiding the problems associated with bovine thrombin, albeit activated factor XIII may be required. (It should be noted that if noncrosslinked fibrin I is utilized such that the noncrosslinked fibrin I comes into contact with patient's blood, for example, on a **wound**, the patient's thrombin and factor XIII may convert the fibrin I to crosslinked fibrin II.)

PI US 5763411 19980609

L16 ANSWER 18 OF 25 USPATFULL

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SUMM Fibrin I monomer is preferred because it can, in contrast to **fibrinogen**, readily be converted to fibrin polymer without the use of thrombin or factor XIII. In fact, the fibrin I monomer can spontaneously form fibrin I polymer, which can act as the fibrin clot, regardless of whether the fibrin I polymer is crosslinked or noncrosslinked or further converted to fibrin II polymer. Thus, since the formation of the fibrin I polymer from fibrin I monomer is spontaneous, the fibrin I polymer can be formed without thrombin and factor XIII, thereby avoiding the problems associated with bovine thrombin. (It should be noted that if fibrin I monomer is utilized such that the fibrin I monomer comes into contact with patient's blood, for example, on a **wound**, the patient's thrombin and factor XIII may convert the fibrin I polymer to crosslinked fibrin II polymer.)

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PI US 5763410 19980609

L16 ANSWER 19 OF 25 USPATFULL

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DETD Fibrin I monomer is preferred because it can, in contrast to **fibrinogen**, readily be converted to fibrin polymer without the use of thrombin or factor XIII. In fact, the fibrin I monomer can spontaneously form fibrin I polymer, which can act as the fibrin clot, regardless of whether the fibrin I polymer is crosslinked or noncrosslinked or further converted to fibrin II polymer. Thus, since the formation of the fibrin I polymer from fibrin I monomer is spontaneous, the fibrin I polymer can be formed without thrombin and factor XIII, thereby avoiding the problems associated with bovine thrombin. (It should be noted that if fibrin I monomer is utilized such that the fibrin I monomer comes into contact with patient's blood, for example, on a **wound**, the patient's thrombin and factor XIII may convert the fibrin I polymer to crosslinked fibrin II polymer.)

DETD Noncrosslinked fibrin I is preferred because it can more readily, as compared to **fibrinogen**, be converted to crosslinked fibrin. In fact, it is believed that fibrin I can form crosslinked fibrin I, which can act as the fibrin sealant. Thus, the formation of the crosslinked fibrin I from noncrosslinked fibrin I can be carried out without thrombin, thereby avoiding the problems associated with bovine thrombin, albeit activated factor XIII may be required. (It should be noted that if noncrosslinked fibrin I is utilized such that the noncrosslinked fibrin I comes into contact with patient's blood, for example, on a **wound**, the patient's thrombin and factor XIII may convert the fibrin I to crosslinked fibrin II.)

PI US 5750657 19980512

L16 ANSWER 20 OF 25 USPATFULL

SUMM The **fibrinogen** component of the fibrin sealant is **prepared** from pooled human **plasma**. The **fibrinogen** can be concentrated from the human **plasma** by cryoprecipitation and **precipitation** using various reagents, e.g., polyethylene glycol, ether, ethanol, ammonium sulfate or **glycine**. For an excellent review of fibrin sealants, see M. Brennan, Blood Reviews, 5:240-244 (1991); J. W. Gibble and P. M. Ness, Transfusion, 30:741-747 (1990); H. Matras, J. Oral Maxillofac Surg., 43:605-611 (1985) and R. Lerner and N. Binur, J. of Surgical Research, 48:165-181 (1990).

SUMM Fibrin I monomer is preferred because it can, in contrast to **fibrinogen**, readily be converted to fibrin polymer without the use of thrombin or factor XIII. In fact, the fibrin I monomer can spontaneously form fibrin I polymer, which can act as the fibrin clot, regardless of whether the fibrin I polymer is crosslinked or noncrosslinked or further converted to fibrin II polymer. Thus, since the formation of the fibrin I polymer from fibrin I monomer is spontaneous, the fibrin I polymer can be formed without thrombin and factor XIII, thereby avoiding the problems associated with bovine thrombin. (It should be noted that if fibrin I monomer is utilized such that the fibrin I monomer comes into contact with patient's blood, for example, on a **wound**, the patient's thrombin and factor XIII may convert the fibrin I polymer to crosslinked fibrin II polymer.)

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PI US 5739288 19980414

L16 ANSWER 21 OF 25 USPATFULL

SUMM There are numerous potential advantages, relative to the use of synthetic materials, associated with the use of **fibrinogen** as an adhesive, sealant or hemostatic agent. For example, when applied to a **wound**, polymerized **fibrinogen** (fibrin) forms a network or scaffolding through which it is more likely that immunologically active cells (to defend against invading pathogens) and also epithelial cells (for tissue regeneration and repair) can migrate. Additionally, fibrin materials may be dissolved gradually by the body (a process termed fibrinolysis) after treatment leading to more normal appearance of the healed site.

DETD One example of how a low molecular weight solute can produce a physiologically incompatible effect has been mentioned, that is, by creating at the concentration thereof that is proposed to be used, an osmotic imbalance between a grafted tissue and a graft bed site interfering therefore with adhesion and/or healing at the site of treatment. Additionally, the substance may cause other deleterious effects at a treatment site, or at a site remote therefrom, such as to affect adversely **wound** healing, or to act as a barrier to physiological processes such as cell migration associated with tissue repair. The existence of such effects, for each potential solute, is well known in the art. Representative of solutes known to the biochemical art as effective solubilizing agents for **fibrinogen** protein but that are incompatible (at **fibrinogen**-solubilizing concentrations thereof) with clinical use are urea at about 500 mM or more; and sodium dodecyl sulfate at about 1% (w/v) or more.

DETD The therapeutic compositions of the invention are **prepared** using a process that comprises, generally, the steps of (A) **precipitating fibrinogen** from mammalian blood **plasma** with polyethylene glycol 1000; and then (B) resuspending said **fibrinogen** in solution; and then (C) reprecipitating said **fibrinogen** with **glycine**; wherein **precipitation** of said **fibrinogen** with said polyethylene glycol was performed only once. More specifically, therapeutic **fibrinogen** -containing compositions of the invention were **prepared** following the procedure described in Example 1 below. Although the above-described effective methods are novel and nonobvious when viewed as a whole, individual steps thereof provide also important contributions to the clinical utility of **fibrinogen** product derived therefrom.

DETD The mixture formed from a **fibrinogen**-containing therapeutic composition and an additional thrombin composition define, according to the practice of the invention, a "reactive therapeutic composition" which contains, typically, and per milliliter thereof in contact with a site of treatment in a patient, between about 0.05 and 500 NIH units of thrombin and between about 7.5 and about 30 mg of **fibrinogen**. The selection of the particular concentration of **fibrinogen** and of thrombin present in a reactive therapeutic composition to be used

in a particular clinical application, and for a particular patient, is guided by factors well known in the medical art including the size of the treatment site and the nature of the procedure to be effected. For example, if the **fibrinogen**-containing composition is used to effect rapid hemostasis at a large **wound**, it is generally appropriate to use a high concentration of thrombin in relation to **fibrinogen** (for example, about 500 units per ml of solution containing about 25 mg of **fibrinogen**) such that the fibrin clot is formed "immediately", that is, within seconds. Additionally, use of up to about 2000 to 3000 units of thrombin per ml of a **fibrinogen**-containing solution is known and is within the practice of the invention. However, if adhesion of a grafted tissue is being performed, wherein careful placement thereof and follow-up manipulation are required, a lower rate of polymerization may be effected using, for example, about 10 units of thrombin per ml of solution containing about 25 mg of **fibrinogen**.

DETD Lyophilized **fibrinogen** compositions of the invention can also be used directly in powder form as a sealant, adhesive or local hemostatic agent. If the lyophilized preparation is to be used in this fashion, it may be sprinkled directly, for example, onto a **wound** site or surgical incision where it reacts with endogenous thrombin to effect a seal or hemostasis. This is typically useful when the site (for example, a vessel or **wound**) to be closed is small, and blood loss is not rapid.

DETD Additionally, the **fibrinogen** composition and/or thrombin may be applied, for example, to a **wound** or surgical incision by incorporation into a gauze pad, sponge, collagen or gel-type matrix or into a similar device and treating the area to initiate hemostasis or adhesion as necessary.

PI US 5605887 19970225

L16 ANSWER 22 OF 25 USPATFULL

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fibrinogen with **glycine**; wherein **precipitation** of said **fibrinogen** with said polyethylene glycol was performed only once. More specifically, therapeutic **fibrinogen** -containing compositions of the invention were **prepared** following the procedure described in Example 1 below. Although the above-described effective methods are novel and nonobvious when viewed as a whole, individual steps thereof provide also important contributions to the clinical utility of **fibrinogen** product derived therefrom.

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SUMM Additionally, the **fibrinogen** composition and/or thrombin may be applied, for example, to a **wound** or surgical incision by incorporation into a gauze pad, sponge, collagen or gel-type matrix or into a similar device and treating the area to initiate hemostasis or adhesion as necessary.

PI US 5330974 19940719

L16 ANSWER 23 OF 25 USPATFULL

SUMM Tissue adhesives are made of human or animal blood or plasma and serve to physiologically glue tissue or bone parts, seal **wounds**, stop bleedings and to promote **wound** healing. They contain, as active components, **fibrinogen** and Factor XIII and, if desired, may contain additional plasma proteins, such as, e.g., fibronectin, albumin, plasminogen activator inhibitors and/or plasma inhibitors, as well as further additives.

SUMM With preparations that are destined for infusion purposes, it is possible to compensate losses in the biologic activity by accordingly higher dosages, which affects the economy, yet not the efficacy of the

products. With tissue adhesives, however, it is not possible to compensate for a reduced biologic activity (expressed by the content of intact soluble **fibrinogen** clottable with thrombin and by the ability of crosslinking of the thus formed fibrin) by a higher dosage. For, an adhesion will by no means become stronger by using more adhesive of lesser quality. Moreover, it is known that crosslinked fibrin stimulates the growth of fibroblasts and, thus, the healing of **wounds**, while **fibrinogen** or non-crosslinked fibrin hardly exhibit this desired effect (S. Kasai, T. Kunimoto, K. Nitta: "Cross-Linking of Fibrin by Activated Factor XIII Stimulates Attachment, Morphological Changes and Proliferation of Fibroblasts", Biomed. Res. 4, 155-160, 1983).

SUMM This invention aims at avoiding the disadvantages of the known inactivation methods and has as its object to provide a tissue adhesive preparation of human or animal origin, which exhibits a high safety with respect to reproductive filterable pathogens, such as viruses, and whose biologic activity is largely preserved, i.e., generally to a value greater than 70% as compared to the untreated tissue adhesive preparation, which means that the **fibrinogen**, in a high concentration, remains soluble and clottable with thrombin and the formed fibrin exhibits a high crosslinking ability. In particular, a sufficient strength of the gluing site and a rapid **wound** healing without complications are to be ensured upon **wound** treatment with the tissue adhesive prepared according to the invention.

DETD A tissue adhesive **preparation** was **prepared** in a known manner according to the method described in U.S. Pat. No. 4,414,976: 277 l human fresh **plasma** frozen at -20.degree. C. were heated to +2.degree. C., the resulting cryoprecipitate was separated by centrifugation and treated with a buffer solution having a pH of 6.5 and containing 6.6 g Na.sub.3 citrate.2H.sub.2 O, 3.4 g NaCl, 10.0 g **glycine**, 25,000 KIU aprotinin and 200 I.U. heparin per liter, and was centrifuged a second time at +2.degree. C. The separated **precipitate** was dissolved in a further buffer solution having a pH of 7.9 and containing 19.0 g human albumin, 9.0 g **glycine**, 1.0 g trisodium citrate.2H.sub.2 O, 25,000 KIU aprotinin and 200 I.U. heparin per liter, and was adjusted to a protein concentration of 50 g per liter. This solution was sterile filtered, filled into final containers (vials) of 12.5 ml each, deepfrozen and lyophilized. In the thus obtained **preparation**, the ratio of Factor XIII to **fibrinogen**, expressed in units Factor XIII per gram fribrinogen, amounted to 109; the water content (residual moisture) of the **preparation** was less than 0.01 (1% by weight).

PI US 4816251 19890328

L16 ANSWER 24 OF 25 USPATFULL

AB A dry preparation having a foam-like and, respectively, fleece-like structure obtained by freeze-drying consists, apart from thrombin in at least catalytically active amounts, substantially of approx. 10 to 95% by weight of fibrin and approx. 5 to 90% by weight of **fibrinogen** . For the preparation thereof, fibrin is produced in situ in an aqueous solution containing **fibrinogen** and thrombin and the resultant reaction mixture is deep-frozen and lyophilized. As further constituents of the dry preparation active substances such as e.g. antibiotics, natural bone material and/or a synthetic, bone-forming substitute, glycoproteins, coagulation-conducive substances and the like and/or fibrinolysis inhibitors come into consideration. The dry preparation is provided mainly for use as a **wound** toilet material, as a filling material for bone cavities and/or as a supporting material for further active substances.

SUMM The present invention relates to a **fibrinogen**-containing dry preparation having a foam-like and fleece-like structure, respectively, obtained by freeze-drying. Such a dry preparation, which is completely

resorptive, may in particular be used as a **wound** toilet material, as a filling material for pathological bone cavities and/or as a supporting material for further active substances conducive to a healing process. Furthermore, the invention relates to a process of manufacturing this dry preparation and to the use thereof.

SUMM A dry preparation of the mentioned type is known from the German Laid-Open Patent Application No. 30 37 513, which concerns a collagenic **wound** cover obtained by freeze-drying of a solution containing both collagen and **fibrinogen**. The resultant dry material may additionally contain a pharmaceutically-active substance such as an antibiotic. A considerable content of collagen in a **wound** cover--especially when the same shall be resorbed--may be harmful, as will be shown in the following.

SUMM Furthermore, a lyophilized tissue adhesive (cf. German Laid-Open Patent Application No. 30 02 934) is known which substantially--apart from a fibrinolysis inhibitor and factor XIII--may consist of **fibrinogen** and albumin and additionally contain glycine, glucose and heparin. However, this tissue adhesive shall not be applied onto the **wound** in the form of a dry preparation but shall be reconstituted by adding water so as to obtain a concentrated **fibrinogen** solution to which then thrombin and CaCl.sub.2 are added.

SUMM If, however, under comparable conditions, an aqueous **fibrinogen** solution were processed by freeze-drying to obtain a dry preparation, a protein plate having a foam-like structure would be obtained which breaks and crumbles easily. Due to its insufficient mechanical strength, such a plate would be unsuited as a **wound** toilet material and/or supporting material for pharmaceutical active substances.

SUMM In spite of their haemostatic effect and high stability (mechanical strength, storage stability), freeze-dried and other collagen products have not been entirely satisfactory in practice when being used as a **wound** toilet material and/or resorptive implant. Drawbacks are e.g. the long residence time of up to six weeks and more in the **wound** area and undesired effects of collagen on certain healing processes, e.g. in the case of bone fractures. Frequently, known collagen preparations have been denatured in the course of their separation from natural material and their preparation, so that this has resulted in an insoluble preparation having a poor resorption behaviour. In contrast thereto, readily soluble collagen preparations always contain salts causing an acidic pH. After introduction into a **wound**, such collagen preparations, in their turn, cause therein an acidic environment, the neutralization of which is an unnecessary burden to the organism and impairs the healing process. It is exactly **wound** healing and the thrombin-induced fibrin formation from present soluble **fibrinogen** which require for their optimum progress an environment having a physiological pH of approx. 7.36. Finally, in the **wound** area collagen is already present in the endogenic structures, tissues and fluids in a physiologically utilizable form so that a considerable additional collagen offer is neither necessary nor desirable.

SUMM Natural **wound** closure material is a fibrin of gel-like state formed from **fibrinogen** and still having a large content of native **fibrinogen**. The in vitro provision of a dry preparation which is more similar to the natural **wound** closure material than conventional dry collagen preparations and which nevertheless has the advantageous properties of such collagen preparations, such as e.g. high mechanical strength, good absorptive capacity and great fluid-retaining capacity as well as unlimited storage stability at room temperature, would lead to a considerable improvement in medical care.

SUMM Based thereon, it is the object of the present invention to provide a **fibrinogen**-containing dry preparation of the above-specified kind, which is entirely or substantially free from collagen and nevertheless has the advantageous properties of common collagen preparations, which, regarding its composition, its physiological properties and its resorption behaviour is more similar to natural **wound** closure material and which is directly, i.e. without any further manipulations such as e.g. the addition of additional and/or activating components, applicable onto the **wound** and effects an accelerated haemostasis at the **wound**.

SUMM The invention is based on the observation that by freeze-drying of a reaction mixture which, apart from **fibrinogen** and at least catalytic amounts of thrombin, contains fibrin formed in situ, a dry preparation is obtained which has a surprisingly high stability, comparable with the stability of freeze-dried collagen products. Even without the addition of further substances and factors conducive to blood coagulation, such a dry preparation has a particularly high hemostatic activity, especially due to the additional offer of active thrombin and **fibrinogen**. Preferably, the fibrin offered with the dry preparation and formed in situ is an especially dimerized fibrin of high biological activity, which is cross-linked only in its longitudinal direction, i.e. is linked substantially only through its .gamma.-chains, and which is used as a starting point for a further and intensified fibrin formation in the **wound** area. With the dry preparation according to the invention a component mixture may be offered which is very similar to the natural **wound** closure material and which consequently is readily adopted by the organism and completely resorbed. A dry preparation formulated in accordance with the invention as a **wound** closure material, e.g. in the form of a fleece having a thickness of 6 to 20 mm, can also stop heavy haemorrhages within a short time, approx. within 2 min.

SUMM According to an alternative process it is not necessary first to isolate the **fibrinogen** in pure, solid form and then to add it to an aqueous solution. E.g., the sediment described in connection with the above-mentioned **fibrinogen** isolation and obtained after the glycine precipitation may be dissolved in an 0.9% aqueous NaCl solution and adjusted to the desired degree of concentration, and, as will be explained in the following, the further additives may be added directly to this solution. Also other **fibrinogen** solutions are suited, for the preparation of which the raw **fibrinogen** has been isolated as a cryoprecipitate from the remaining serum with its proteins and factors, e.g. according to the process of the German Laid-Open Patent Application No. 30 02 934. What is important is a far-reaching isolation of the enzymes and/or factors causing the spontaneous fibrin formation, so that a considerable content of stabilizing salts such as citrate, phosphate, oxalate or the like is prevented in the initial solution. It is exactly the dry preparation provided as a **wound** closure material which shall provide a component mixture which is very similar to the natural **wound** closure material. In particular for this application unphysiological salt concentrations in the initial **fibrinogen** solution are to be prevented. On the other hand, when providing this initial solution, one may already aim at an enrichment with coagulation factors, e.g. factor XIII. The **fibrinogen** content of such an initial **fibrinogen** solution shall also amount of 10 to 90 mg, preferably to 50 to 80 mg of **fibrinogen** per 1 ml of solution.

SUMM If the dry preparation is to be used specifically as a **wound** toilet material, a freeze-dried fleece of average hemostatic effectiveness may be produced, to which later a highly effective, enriched, powdery plasma derivative is added for accelerated hemostasis

and optimized control of **wound** closure, as will be set out in detail in the following. Alternatively, the essential components of this enriched plasma derivative may be added already to the **fibrinogen** solution. The main constituents of this plasma derivative include **fibrinogen**, thrombin, components of the prothrombin complex and protease inhibitors; furthermore, admixtures of blood platelet extracts, antibiotics and the like may be provided. In particular, an addition of phospholipids, prostaglandines, coagulation factors, antihistamines, vasopressins, growth factors, vitamins and the like may be provided for this purpose. The presence of prostaglandines contributes to the activation of the capillary bed in the **wound** area as well as the activation of the platelets in the blood stream. The blood coagulation factors, e.g. factor XIII, blood platelet extracts and other factors which are necessary for the coagulation of the blood such as e.g. leucotrines, platelet-activating factors, support and increase the effect of the factors present in the body fluid in the sense of an accelerated hemostasis and an optimization of **wound** closure. As the phospholipid preferably a thrombocyte extract obtained from human whole blood is used. Further suitable phospholipids are e.g. extracts from cerebral matter. The coagulation factors VIII and IX are used for hemophilic **wound** toilet. An additive of adrenaline and/or ergotamine has a vasoactive effect, which finally leads to an accelerated coagulation of the blood. With regard to their high specific effectiveness, the sum of the proportions of prostaglandines, phospholipids, coagulation factors and the further active substances mentioned mostly is not more than 1.2% by weight, preferably not more than 0.8% by weight of the finished dry preparation. The specified substances, in the mentioned amounts, are also added to the **fibrinogen** solution prior to or together with the addition of thrombin.

SUMM The proportion of added active thrombin depends on various factors. Regarding the process conditions, a high thrombin concentration accelerates the fibrin formation so that in the case of high thrombin concentrations the reaction mixture must be deep-frozen after a relatively short period of time so as still to ensure a sufficient **fibrinogen** content. As regards the end product and the various applications thereof, a relatively high thrombin content is desirable for a **wound** toilet material for accelerating the hemostasis together with the additional **fibrinogen** offer. For producing a **wound** toilet material which has a satisfactory hemostatic effect also without later addition of coagulation-active enzymes and factors, relatively high amounts of thrombin, may be added to the **fibrinogen** solution, e.g. 20 to 30 and more units of thrombin per 1 ml of solution. For other cases of application, e.g. as a supporting material for active substances such as antibiotics, the thrombin content of the end product is of minor importance; in this case, a small thrombin addition will be sufficient which is enough for reacting the provided **fibrinogen** into fibrin to the desired high amount of more than 50% within adequate periods of time. In this case, catalytically active amounts of thrombin of at least 0.1 unit, preferably of approx. 5 to 10 units per 1 ml of **fibrinogen** solution, will be sufficient.

SUMM If there are no unphysiologically high salt and/or stabilizer concentrations, thrombin generates from **fibrinogen** fibrin monomers which are polymerizable in an aqueous medium. The nature of the polymer obtained from these monomers depends on various factors. If the **fibrinogen**-and thrombin-containing formulation were left to itself, the entire **fibrinogen** would be reacted after approx. 4 to 6 hours and a stiff gel would be obtained which, when being shaken, collapses into fibrin filaments. In this case, the polymerization takes place through the .alpha.- and .gamma.-chains of the fibrin monomers. If the resultant precipitate were lyophilized, a hard, brittle product

would be obtained, which is less suited as a **wound** toilet material due to its low mechanical strength and flexibility as well as its reduced solubility and delayed degradability.

SUMM Thus, according to the invention of the fibrin contained in the dry preparation is prepared in situ in an aqueous medium containing **fibrinogen** and thrombin. The fibrin formed in this manner proves to be much more native, soluble and purer than e.g. the fibrin according to the U.S. Pat. No. 3,523,807, which by CaCl.sub.2 precipitation is precipitated from human plasma and separated. The latter material is practically insoluble, contains inclusions of other plasma proteins and thus is less suited for application as a **wound** toilet material.

SUMM According to the most general embodiment of the invention, the fleece, apart from thrombin in at least catalytically active amounts, shall substantially consist of approx. 10 to 95% by weight of fibrin and approx. 5 to 90% by weight of **fibrinogen**. By "at least catalytically active amounts" a thrombin content of approx. 0.1 to 10 units, preferably of 3 to 8 units, per 1 cm.sup.3 of fleece material is meant. These "units" are the "NIH-units" (according to the standards of the National Institute of Health of the United States) common among those skilled in the art. In the case of a fibrin content of less than 10% by weight, the **fibrinogen** nature of the dry preparation is prevailing so that the material is brittle and has an insufficient mechanical strength. Therefore, the fibrin content shall amount to at least 10% by weight, preferably at least 30% by weight of the dry preparation. Fibrin contents of more than 95% by weight require reaction conditions which yield a solid material of physiologically low activity, which can be dissimilated by the organism only with difficulties. Therefore, the fibrin content shall not amount to more than 95% by weight, preferably not more than 70% by weight, of the weight of the fleece. A dry preparation having a fibrin content of approx. 20 to 30% by weight and a **fibrinogen** content of approx. 80 to 70% by weight, after moistening with body fluid, yields a preparation which is particularly similar to the natural **wound** closure material and thus is preferred especially.

SUMM If the dry preparation according to the invention mainly is to be used as a hemostatic and vulnerary **wound** toilet material, the fleece shall predominantly consist of **fibrinogen**. In this case, a fibrin content of approx. 10 to 40% by weight and **fibrinogen** content of approx. 60 to 90% by weight has proven to be particularly suited. On being moistened with the exudation of a **wound**, the **wound** toilet material shall take up the fluid, partially dissolve and form a highly viscous, sticky paste which adheres to the **wound** area, withstands the pressure of the escaping blood and activates the coagulation enzymes of the contacting blood. For this activation preferably coagulation-conducive substances, vaso-active substances, coagulation factors and the like are additionally offered with the dry preparation. These components may be introduced already into the solution used for the manufacture of the dry preparation and, together with the same, be deep-frozen and lyophilized. It is an advantage of this alternative that the components are most finely distributed within the dry preparation, which even further increases the effectiveness thereof. Alternatively, these components may belatedly be incorporated in the form of a powdery combination of active substances into the dry preparation substantially consisting only of thrombin, fibrin and **fibrinogen**. This permits the presence of active substances the activity of which is impaired by the freeze-drying and/or extraordinarily high thrombin concentrations which due to the accelerated fibrin formation would impair the process in other respects.

SUMM A suitable powdery biochemical substrate for accelerated hemostasis and

optimized biochemical control of **wound** closure, which in powdery form may be applied onto the preformed dry preparation according to the invention, is described in detail in the European Patent Application No. 8 111 0615.2 of Dec. 18, 1981. As far as necessary, the content of this European Patent Application shall be incorporated into the present papers by reference. This powdery, biochemical substrate is formulated with regard to an optimized activation of the exogenic and/or endogenic coagulation system as well as under consideration of a multiplicity of physiological and pathological factors. This substrate contains inter al. **fibrinogen**, thrombin, components of the prothrombin complex, protease inhibitors. Depending on the purpose of application, additionally blood platelet extracts, antibiotics and the like may be added at suitable mixing ratios. A preferred embodiment of this plasma derivative consists substantially of 80 to 94% by weight of **fibrinogen**, 1 to 10% by weight of thrombin and/or prothrombin and 0.01 to 3% by weight of fibrinolysis inhibitor contains less than 0.4% by weight of cryo-insoluble globulin and, moreover, may additionally contain phospholipids, prostaglandines, desiccants and stabilizers, antibiotics and/or blood coagulation factors, all in solid, powdery form. This highly effective, powdery combination of active substances may be applied in amounts of approx. 0.1 to 5 parts by weight per 100 parts by weight of dry preparation. Preferably, these small amounts are blown onto the surface of the dry preparation by means of a sterile gas jet and adhere thereto in sufficient amount. The fibrin/ **fibrinogen** fleece obtained thereafter may directly be used for **wound** treatment or be integrated into a first-aid bandage (adhesive plaster). Thus, a **wound** toilet material is obtained which has on the surface of an exclusively biological supporting material a highly effective active substance combination for accelerated hemostasis and optimized biochemical control of **wound** closure.

DETD 5 g of **fibrinogen** (microcrystalline **preparation** obtained from human **plasma** by alcohol/**glycine precipitation**, as specified above) are dissolved in 100 ml of 0.9% NaCl solution so as to obtain a resultant final concentration of protein of 50 mg/ml. 300 units of thrombin ("Topostasin" of the company Hoffmann LaRoche AG, Grenzach-Wyhlen) are added to the **fibrinogen** solution with agitation. Agitation is continued for a short time, and then the entire formulation is poured into a lyophilization mold and held at room temperature for further 20 min. Thereupon, deep-freezing follows, i.e. the entire formulation including the mold is cooled to approx. -40.degree. C. within 10 min. Thereupon, the formed ice block is lyophilized; for this purpose, the vapour phase is continuously pumped off under vacuum and freeze-separated. Thereby, a mixture of **fibrinogen** and soluble fibrin in the form of a loose, continuous protein fleece is obtained, which has a good mechanical and breaking strength. Apart from catalytically active amounts of thrombin, this dry **preparation** consists of approx. 20% by weight of fibrin and 80% by weight of **fibrinogen**. The following investigations were made with this dry **preparation**:

DETD For application as a **wound** toilet material the **fibrinogen**/fibrin fleece is cut to dimensions of 8.times.50.times.100 mm and sterilized. In case of need, the product is placed onto the **wound** area. Due to the absorption of the exudation of the **wound**, the coagulation of the escaping blood is initiated.

DETD 5 g of **fibrinogen** are dissolved in 100 ml of 0.9% NaCl solution containing 0.025 M of CaCl.sub.2. 1,0 g of albumin and 500 units of factor XIII are added to the formulation. As an antibiotic, the material shall contain 1 million units of Baycillin, which are added to the solution in the form of a powder. 100,000 units of aprotinin serve to prevent a premature lysis of the **wound** toilet material in the **wound** area. The inhibitor is also added to the solution in the form of a powder. By adding 30,000 units of thrombin, the fibrin

formation is allowed to start, wherein the formulation exists already in dry form. After a reaction time of 1 hour, the material is freeze-dried. The adding of factor XIII increases the degree of cross-linkage of the fibrin and contributes to the stability of the fleece.

CLM What is claimed is:

1. **Fibrinogen**-containing dry preparation having a foam-like and fleece-like structure, especially adapted for use as a **wound** toilet material, filling material for bone cavities, and/or supporting material for further active substances, consisting essentially of thrombin in an at least catalytically active amount, about 10 to 95% by weight of fibrin, and about 5 to 90% by weight of **fibrinogen**.

3. Dry preparation according to claim 1, wherein the fleece is adapted mainly for use as a hemostatic and vulnerary **wound** toilet material, has a thrombin content of at least 1 NIH unit of thrombin per 1 cm.sup.3 of fleece material, and contains about 10 to 40% by weight of fibrin, about 60 to 90% by weight of **fibrinogen**, and about 0 to 1.2% by weight of a material selected from the group consisting of coagulation-conducive substances, vaso-active substances, and coagulation factors.

4. Dry preparation according to claim 1 or 2, wherein the fleece is adapted mainly for use as a hemostatic and vulnerary **wound** toilet material, consists essentially of about 10 to 40% by weight of fibrin and about 60 to 90% by weight of **fibrinogen**, and comprises, incorporated into said fleece, a powdery enriched plasma derivative which is a combination of substances which accelerate hemostasis and optimize biochemical control of **wound** closure.

16. Method of using the dry preparation according to any of claims 1, 2 or 3 for accelerated hemostasis and optimized biochemical control of **wound** closure, comprising the step of applying onto the fibrin/ **fibrinogen** fleece a powdery active substance combination containing **fibrinogen**, thrombin, components of the prothrombin complex, protease inhibitors, blood platelet extract and/or an antibiotic, and applying the thus-treated fleece to the **wound**.

PI US 4442655 19840417

L16 ANSWER 25 OF 25 USPATFULL

SUMM Plasminogen is a protein that plays a central part in the fibrinolytic activity of the plasma. It represents the zymogen of plasmin, which latter is a protease having a great specificity for fibrin and **fibrinogen**. Upon completion of a thrombus formation and after the healing of a **wound** has started, the fibrin clot is decomposed by plasmin by local proteolysis. Plasminogen deficiencies, for example as may occur temporarily during fibrinolysis therapy, may be combated successfully with plasminogen concentrates.

SUMM It is known to remove prothrombin, to which the instability of the blood coagulation factors is attributed from **plasma** fractions with absorbents or **precipitation** agents. This applies particularly to the fraction that contains factor VIII. It is moreover known to **precipitate** factor VIII in conjunction with **fibrinogen** using **glycine**, to use suitable amino acids, in particular .beta.-alanine, for a partial separation of the **fibrinogen** from factor VIII and to use mineral absorbents that are capable of binding impurities accompanying the factor VIII **preparation** under certain circumstances.

SUMM To **prepare** a hepatitis-safe **preparation**, heating for 10 to 20 hours to 60.degree. C. to 70.degree. C. in the presence of saccharose in a concentration from 40 to 60 w/w % and of **glycine** of from 1.0 to 2.5 mols/l is required. Suitably, fractions in which the

factor to be stabilized is enriched according to the cited processes are used. For example, to **prepare** a factor VIII **preparation** a fraction obtained according to the so-called method IV (Cohn, J. Amer. Chem. Soc., 68, 459 et seq, (1966) is used. This fraction is **precipitated** from **plasma** using 8 v/v % of ethanol under the conditions as specified by Cohn. It contains **fibrinogen** and factor VIII in addition to various globulins. Moreover, the so-called "cryoprecipitate" which is obtained by a cold **precipitation** of **plasma** according to J. G. Pool et al. [New England J. Med. 273, 1443-1447 (1965)] may be used as a starting material. To obtain the cryoprecipitate, fresh **plasma** is first brought to a temperature of -30.degree. C. and of +4.degree. C. and then the resulting residue is recovered. Each of said **precipitates** contains more or less prothrombin, which can be readily activated and to which the loss in activity of factor VIII **preparations** is attributed. It is, therefore, advisable to remove the prothrombin prior to applying the process according to invention, for example by absorption on aluminum hydroxide or on barium sulfate, by **precipitation** with acridine bases or by chromatography on ion exchanger resins. Aluminum hydroxide in gel suspension is preferably used.

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L1          2233 S FIBRINOGEN AND WOUND
L2            92 S L1/CLM
L3            40 S L1/AB
L4            21 S L2 AND L3
L5          1989 S FIBROBLAST AND FIBRINOGEN
L6            26 S FIBROBLAST MIGRATION AND FIBRINOGEN
L7             0 S L4 AND L6
L8          8067 S FIBRINOGEN
L9           116 S PREPAR? (2S) L8 (3S) GLYCIN?
L10          115 S PREPAR? (1S) L8 (1S) GLYCIN?
L11            0 S PREPAR? (1S) L8 (1S) GLYCIN?  (1S) PLAMA
L12           69 S PREPAR? (1S) L8 (1S) GLYCIN?  (1S) PLASMA
L13           43 S L12 (1S) PRECIPITAT?
L14           28 S L13 AND L1
L15          623 S FIBRINOGEN (1S) WOUND
L16           25 S L15 AND L13

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SACE IS NOT A RECOGNIZED COMMAND
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For a list of commands available to you in the current file, enter
"HELP COMMANDS" at an arrow prompt (=>).

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ENTER NAME OR (END):fibrinogen/a
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